FEB 8 1935

VOL. 189, No. 2 FEBRUARY, 1935 No. 755

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

FEBRUARY, 1935

ORIGINAL ARTICLES.

THE CHANGING CAUSE OF DEATH IN DIABETES MELLITUS.

By John M. Flynn, M.D.,
JUNIOR ASSOCIATE IN MEDICINE, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Medical Clinic of the Peter Bent Brigham Hospital.)

With the discovery of insulin, in 1922, the treatment of diabetes mellitus was placed upon a new basis. Fitz and Murphy,[1] of the Peter Bent Brigham Hospital, anticipating that the clinical picture and course of the disease might be changed to a considerable degree by the newer method of treatment, analyzed the records of all the cases of diabetes mellitus which had died in that institution between the time when it opened, in 1913, and the commencement of the insulin era, in 1923. Their conclusions may be summarized as follows:

1. The annual mortality of new cases varied so much from year to year as to make conclusions with regard to the value of treatment, as it affected the hospital mortality of diabetes during any one year, of but little value.

2. Diabetes became less severe as the age at which symptoms were first recognized became greater, although increasing years did not necessarily preclude a severe form of the disease.

3. There were four common causes of death. These were: (*a*) Coma with or without a terminal infection; (*b*) sepsis; (*c*) cardiovascular renal disease, including gangrene; (*d*) pulmonary tuberculosis.

Coma and pulmonary tuberculosis tended to occur more frequently in the younger patients; cardiovascular renal disease, including gangrene, in the older ones, and sepsis in those of any age.

The present paper is written by way of contrast to the earlier one, in an effort to determine whether any radical change in the clinical manifestations of diabetes has become apparent during the last decade since the introduction of this new therapeutic agent.

The Hospital Mortality of Diabetes. The diagnosis of diabetes mellitus was made in 562 cases admitted for the first time from the opening of the hospital, in 1913, until the end of 1922, and of these, 49 died in the hospital. From the beginning of 1923 to the close of 1933, 917 cases were admitted for the first time, and of these 66 died in the hospital. Thus the mortality rate of diabetes among new cases has remained nearly constant in spite of insulin, decreasing only from 9% during the pre-insulin period to 7% in the period during which insulin has been in use.

Study of the present series of cases confirms the conclusion of Fitz and Murphy in regard to the inconstancy of the hospital mortality of diabetes from year to year. In order to make this clear, the number of new cases admitted each year has been tabulated, and the number of deaths occurring among them (Table 1).

TABLE 1.—THE VARIABILITY OF DIABETIC MORTALITY.

Year.	New cases admitted.	New cases dying in hospital.	Mortality per 100 cases.
1923	133	11	8
1924	103	7	7
1925	91	2	2
1926	84	8	10
1927	97	4	4
1928	74	6	8
1929	69	8	11
1930	81	10	12
1931	59	6	10
1932	58	1	1
1933	68	3	4
Total	917	66	
Average	83	6	7

The annual mortality for the new cases in the last 11 years has varied between 1% and 12%, with an average annual mortality of 7%. In the previous decade Fitz and Murphy noted a variation between 2% and 12% in the mortality rate during the different years, but with an annual average of 9%. They explained such variability by the fact that diabetes may be either a very mild or a severe type of disease. Any form of hospital treatment will appear to be accompanied by a low immediate mortality, if a sufficient number of mild cases is treated. On the other hand, a small series of severe cases will exaggerate the inevitable mortality which accompanies any chronic disease requiring hospital care. With as few cases as here reported, the sampling necessarily will be inadequate and fail to level out annual variations. This would be true of any disease with varying severity in individual cases.

The Duration of Diabetes in Fatal Cases. Of the 66 fatal cases in the present series, 48 were able to date the onset of their disease with a fair degree of accuracy. Thus the duration of diabetes was estimated and the results were arranged according to the age at the time of death (Table 2):

TABLE 2.—THE DURATION OF DIABETES.

Age at death.	Total number of cases.	Total duration of diabetic life, yrs.	Average duration of diabetic life, yrs.	Shortest duration of diabetic life, yrs.	Longest duration of diabetic life, yrs.
61 to 80	17	97 6	5 7	0 3	20
51 to 60	20	118 0	5 9	0 3	30
41 to 50	4	14 6	3 6	0 6	8
21 to 40	6	16 0	2 7	1 0	6
Less than 21	1	1 0	1 0	1 0	1
Total series	48	247 2	5 1		
Series, Fitz and Murphy	55	225 0	4 1		

This table illustrates the well-known fact that diabetes tends to become less severe as the age at which symptoms are first recognized becomes greater. On the other hand, it also illustrates the fact that acute diabetes now as formerly may develop in persons of almost any age, so that increasing years do not necessarily preclude a severe form of the disease. The situation as here reported, however, differs in two important respects from that of 11 years ago. The most striking feature to be observed in a comparison of the two groups of cases is that fatalities in the younger age group now appear to be much less frequently met with than formerly. The previous study showed 21 deaths in persons below their 40th year, whereas the present study shows but 7 or, in terms of percentage, 38% of the deaths in the earlier series occurred in patients below 40, while but 14% of the younger cases in the present series have been fatal. This without doubt is due to insulin.

A second point which seems worthy of mention is that in the age group from 61 to 80 the average duration of diabetic life was 8.1 years in the earlier series and is 5.7 years in the present study. The apparent increase in the severity of diabetes in old people is of considerable interest. Perhaps the figures are misleading and are explainable, in part at least, by the fact that an unusual number of elderly patients in the present series entered the hospital with complications by necessity having a high mortality rate. For example, in the present elderly group there were 5 cases with coronary occlusions, 2 with cancer, 2 with general sepsis and 1 with a ruptured aneurysm. All of these complications might reasonably have proved fatal even if diabetes mellitus had not been present. It is significant, however, that of all the persons in the old age

group but 42% had ever received insulin prior to the hospital admission in which they died. One should not forget that the best modern treatment of even mild diabetes consists in the use of an appropriate diet on which the patients may remain sugar-free and in the proper use of insulin. The experience of this hospital suggests that insulin should be used more frequently in the mangement of elderly diabetics than formerly and that such cases deserve very careful supervision.

The Cause of Death in Diabetes Mellitus. Let us turn to the actual causes of death from which diabetic patients now are likely to succumb. Of the 86 diabetic patients who died in this hospital during the last 11 years, the true cause of death was ascertained by necropsy in 43. There were 2 cases of coma which showed no gross anatomic changes and in which the patients appeared to die from what might be called uncomplicated diabetic coma. There were 12 cases which, with or without coma, had an obvious sepsis or terminating acute infection. There were 3 cases of active pulmonary tuberculosis. There were 5 cases with unusual complications, such as acute nephritis (1 case) and carcinoma (4 cases). There were 21 cases with cardiovascular disease, including gangrene and chronic nephritis. The striking differences between the situation as it is at present and the situation 11 years ago, as reported by Fitz and Murphy, is best shown in tabular form with the figures reduced to a percentage basis:

TABLE 3.—THE CAUSES OF DEATH IN DIABETES MELLITUS AS PROVED BY NECROPSY.

	1913–1922, % of deaths.	1923–1933, % of deaths.
Coma	11	5
Sepsis	38	28
Cardiovascular disease	24	49
Pulmonary tuberculosis	19	7
Unusual complications	8	11

At a glance two striking differences are to be seen between the fate of the pre-insulin diabetic and the diabetic of today. Deaths from coma, sepsis and pulmonary tuberculosis have shown a marked decrease, whereas those due to cardiovascular disease and its sequelæ have shown a marked tendency to rise. Coma, sepsis and tuberculosis accounted for about 70% of the deaths in the pre-insulin diabetics; they account for less than 40% of the diabetic deaths today. On the other hand, cardiovascular disease and its complications have increased in incidence to such a degree that they now account for approximately half of all diabetic deaths, whereas they formerly accounted for but 24%.

It would seem fair to credit the decrease in the incidence of coma and sepsis to the use of insulin. Physiologic studies have shown that insulin brings about complete oxidation of bodies of the ketone group, and these substances are considered to be the chief cause of

diabetic acidosis. By virtue of insulin one may rightfully expect uncomplicated coma to disappear from hospital records as a cause of death in diabetes save in those rare cases where the patient enters the hospital in the moribund state.

The decrease in sepsis may be explained by contrasting the nutritional condition of the diabetic today with that of the diabetic of a dozen years ago. At that time submaintenance diets were required in the treatment of practically all cases of diabetes. As a result of this procedure loss of weight was likely to occur. Today we may stabilize the patient's weight at the optimum by the exhibition of a suitable diet and the proper dose of insulin. In normal people resistance to infection is certainly enhanced by the possession of a body weight in the region of or just above the optimum. There seems to be no reason why similar reasoning should not hold in the case of diabetics.

The decrease in the incidence of tuberculosis as a cause of death in diabetes which was found in this clinic is not substantiated by the exhaustive studies of Root.[2] In a study of 2650 fatal cases of diabetes he found that pulmonary tuberculosis had increased from 4.7% of 342 deaths prior to June, 1919, to 6.7% of 1503 deaths between August, 1922, and November, 1931. The reasons for this increase are still matters of conjecture.

Cardiovascular disease, including gangrene and chronic nephritis, accounted for 24% in the present series. The great increase in deaths arising from this source suggests that the present mode of treatment has no effect whatsoever upon the development of vascular disease in diabetic patients. Many hypotheses may be invoked in order to explain this. One may say that insulin has such a pronounced effect upon coma and sepsis that a large number of diabetic patients live long enough to arrive at the age where vascular disease usually becomes manifest in non-diabetics. The fact that juvenile diabetics are subject to precocious vascular changes would seem to suggest that the arteriosclerotic process seen in these patients is a manifestation of the diabetes itself, rather than part of a separate aging process. Furthermore, the process seems to take place regardless of the exhibition of insulin. Future improvement in therapy should be directed toward this phase of the disease.

Comment. In contrasting the diabetic of today with the diabetic of a dozen years ago, one is gratified at the changes which have taken place. At the time when insulin was first discovered perhaps too much was expected as a result of its discovery. In envisaging its benefits, it was not realized that insulin would unmask a serious defect in diabetic therapy. The marked increase in the mortality arising from cardiovascular complications is probably the most outstanding defect in our present form of treatment. Our knowledge of these cardiovascular complications is by no means complete

at the present time. We know the pathology of these vascular changes, we know that they originate relatively early in the course of the disease, but we do not know their precise cause, and at the present time we know of no method by which we may cure them or prevent their occurrence.

Success in the management of any chronic and incurable disease is measurable:

1. By the prolongation of life.

2. By decreasing the disability due to the disease, and thus making life more endurable for the ones afflicted.

Judged by these criteria the modern forms of diabetic therapy has brought about the following improvements:

1. The average duration of life following the onset of the disease has been prolonged from 4.1 to 5.1 years.

2. The nutritional level of these patients has been raised, so that they no longer need to live in a state of constant discomfort and weakness due to semistarvation.

3. Coma is relatively infrequent, and if it does ensue, the newer mode of treatment will probably overcome it.

4. Sepsis is less frequent than formerly, and when it does supervene, our present method of treatment shows a great improvement over that which was formerly employed.

Conclusions. A study was made of the fatal cases of diabetes mellitus which were observed in this clinic from 1923 to the end of 1933. This was contrasted with the work of Fitz and Murphy, who reported the fatal cases observed here prior to the beginning of 1923.

The present study would appear to justify the following conclusions:

1. In both series of cases there were four common causes of death. These causes are coma, sepsis, pulmonary tuberculosis and cardiovascular disease, including gangrene and chronic nephritis.

2. Since the introduction of insulin, coma and sepsis have decreased in frequency; cardiovascular disease has shown an increase in frequency; unusual complications have remained practically unchanged.

3. The mortality rate of new cases of diabetes in this clinic has decreased from 9% prior to the introduction of insulin to 7% during the period of insulin therapy.

4. The present tendency is for coma and sepsis to be eradicated as a cause of diabetic mortality.

5. Our present mode of treatment appears to have no effect upon the form of cardiovascular disease which is seen in diabetic patients.

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STUDIES IN DIABETES MELLITUS.

III. Interpretation of the Variations in Diabetes Incidence.

By Elliott P. Joslin, M.D.,
CLINICAL PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; MEDICAL DIRECTOR OF THE GEORGE F. BAKER CLINIC, NEW ENGLAND DEACONESS HOSPITAL, BOSTON, MASS.

Louis I. Dublin, Ph.D.,
THIRD VICE PRESIDENT AND STATISTICIAN, METROPOLITAN LIFE INSURANCE COMPANY,

AND

Herbert H. Marks,
NEW YORK CITY.

(From The George F. Baker Clinic, New England Deaconess Hospital, and the Statistical Bureau, Metropolitan Life Insurance Company.)

In two preceding papers[1,2] we have reviewed the increasing incidence of diabetes and its variations according to sex, locality, socio-economic position and other groupings. These variations appear to reflect the interaction of two basic types of forces: constitutional or intrinsic, and environmental or extrinsic. This is evident both from the changing incidence of the disease in the same population over a period of time and in the differences exhibited by various population groups at a given time. Superficially, there would seem to be a distinction between these two types of variations. Actually, however, they are almost identical; for the changes in environmental conditions which favor a high incidence of diabetes are of such a nature as to affect an increasing portion of the population. For the most part, these variations represent real differences in the incidence of the disease but, to a certain extent, they are only apparent in that they represent differences in the known, in contrast to the actual, incidence. The purpose of this paper is to demonstrate the operation of the forces which cause the observed variations, and to distinguish the forces which produce real variations from those which produce apparent variations in the disease.

The data pertinent to the authors' viewpoint are not altogether satisfactory. They are either incomplete or unavailable, and often only indirect or inferential evidence can be offered. Indeed, assembly of fundamental data on certain of the subjects discussed in this paper is urgently needed. It is to be hoped that our admittedly incomplete discussion will stimulate research which will help to clarify those parts which are based on presumptive evidence. Until this is done, it is impossible to prove the authors' viewpoint by rigorous scientific methods. For this reason, largely, the authors have not used the method of correlation analysis to measure the

association between these factors in the changing incidence of the disease. Furthermore, the various factors are often not measurable either in their direct or indirect effects, or the weight of any single factor is so thinly and widely diffused that such methods of computation lead to erroneous or indefinite results.

Constitutional Factors. The chief constitutional feature in the onset of diabetes is overweight. This is clear whether we analyze the weights of known diabetics or take a group of supposedly non-diabetic persons and ascertain the subsequent history of various groups of them according to their weight.

TABLE 1.—MAXIMUM WEIGHT PRIOR TO ONSET OF DIABETES AND WEIGHT AT ONSET OF ADULT DIABETIC PATIENTS (AGES 20 AND OVER).

Percentage in Groups Classified by Deviation from Average Weight for Height and Age. By Sex. Experience of Elliott P. Joslin, M.D., 1898–1928.

Weight group.	Per cent.			
	Previous maximum weight.		At onset.	
	Males.	Females.	Males.	Females.
All cases	100.0	100.0	100.0	100.0
Overweight, total: (5% or more above average)	78.5	83.3	62.7	67.4
20% or more	51.0	59.3	33.8	41.1
40% or more	16.5	25.8	8.6	15.4
30% to 39%	13.9	14.2	9.5	11.2
20% to 29%	20.6	19.3	15.7	14.5
5% to 19%	27.5	24.0	28.9	26.3
Normal weight (less than 5% above or below average)	13.6	10.4	17.9	13.6
Underweight, total: (5% or more below average)	7.9	6.3	19.4	19.0
5% to 19%	7.1	5.5	16.3	14.9
20% or more	0.8	0.8	3.1	4.1
Number of cases	2251	2345	1613	1481

Clinical records show the great frequency of overweight among diabetics. The experience of Joslin (Table 1) is typical. The weight history of all adult diabetic patients, seen from 1898 to 1928, has been analyzed from two points of view: (1) The maximum weight prior to onset of the disease, and (2) weight at onset. Among 4596 patients for whom facts were available, 78.5% of the males and 83.3% of the females were overweight (5% or more above

average for age) at the time of their maximum weight. The weight of onset gave somewhat lower figures. Of the 3094 cases for whom these facts were noted, 62.7% of the males and 67.4% of the females were overweight. Moreover, one-half of the men and close to 60% of the women were at least 20% overweight at their maximum weight. Large numbers were extremely fat. No less than 16.5% of the men and 25.8% of the women were 40% or more overweight at their maximum. In contrast with these high figures, only 7.9% of the men and 6.3% of the women had always been underweight (5% or more less than average for age) and less than 1% of the whole group had always been 20% or more underweight.

The importance of obesity in diabetes is also confirmed by insurance records, which show that its subsequent development among persons accepted for insurance after medical examination and known not to be diabetic is far more frequent among overweights than among persons of average weight or less. Thus, in the Medico-Actuarial Investigation,[3] covering the combined mortality experience of 43 insurance companies, between 1885 and 1909, on men insured at standard premium rates, 3 broad weight groups were distinguished, namely, 50 pounds or more overweight, 25 pounds or more underweight and "standard" weight, falling between these two extremes. Among those insured at ages under 30, the subsequent diabetes death rate of overweights was 15 per 100,000, compared to 6 among "standard" weights and 7 among underweights. Among those between 30 and 45 years when insured, the diabetes mortality was 59 per 100,000 for the overweights, 12 for "standard" weights and 5 for underweights. For those 45 years or over when insured, the diabetes death rate among overweights was 136, compared with 28 for the "standard" group and 6 for underweights. In this study, therefore, a large disparity existed between the diabetes death rates of overweights and persons of average weight or less, and this disparity increased with advancing age. In the recent Medical Impairment Study,[4] an investigation of the same type as the earlier one but covering the experience of 39 companies between 1909 and 1928, similar results were obtained. The findings of these two studies regarding diabetes and weight are summarized in Table 2.

Furthermore, the toll of diabetes increases with the degree of overweight. A study of the experience of the Union Central Life Insurance Company[5] showed that men who were 5 to 14% above average weight had a diabetes mortality only $1\frac{1}{2}$ times that of normal weights, compared with $3\frac{1}{5}$ times for those 15 to 24% overweight, and $8\frac{1}{3}$ times for those 25% or more overweight. These differences were even larger at the ages of 45 and over; those 5 to 14% overweight suffered a mortality nearly twice that of normal weights, and those 15 to 24% overweight, nearly 4 times, while

those 25% or more overweight had a mortality over 10 times that of average weight men.

TABLE 2.—INFLUENCE OF WEIGHT ON MORTALITY FROM DIABETES. DEATH RATES PER 100,000 AMONG MALES ACCEPTED FOR LIFE INSURANCE AT STANDARD RATES. BY WEIGHT AND AGE GROUPS AT ISSUE.

	Supplement to medical impairment study, 1909–1928.			Medico-actuarial mortality investigation, 1885–1909.		
	Ages at issue:			Ages at issue:		
	10 to 29.	30 to 44.	45 and over.	15 to 29.	30 to 44.	45 and over.
Overweight (50 pounds or more above average)	15	19	35	15	59	136
"Standard" (less than 50 pounds above or 25 below average)	4	8	25	6	12	28
Underweight (25 pounds or more below average)	3	3	18	7	5	6

All fat people do not, of course, get diabetes. For example, in the Medico-Actuarial Investigation,[3] only 5% of the deaths of men 50 pounds or more overweight when insured, were due to diabetes. Other factors must be involved in the causation of the disease. Many have been advanced, such as heredity, infections, arteriosclerosis and pluriglandular disturbances. The most significant is probably heredity.* Indeed, the factors of obesity and heredity are probably closely linked. Obese persons who become diabetic appear, for the most part, to be those with an inherited susceptibility to the disease, the obesity acting as the exciting factor to produce the disease. The importance of heredity is brought out by many careful analyses of family histories of diabetic patients, notably the studies of Pincus, White and Joslin[6,7] on Joslin's patients. It is also indicated by Tyner's[8] study of the weights of 500 patients with normal carbohydrate tolerance and 500 with impaired tolerance, but not frankly diabetic. Tyner found that "pre-diabetes" was more common in obese persons than among persons of normal weight only where there was a family history of diabetes.

The authors recognize that the relationship between obesity and diabetes is as yet not clearly defined. Diabetes has not been produced by overfeeding alone, experimentally or otherwise. The nearest approach to this has been the work of Allen,[9] who produced symptoms of the disease by fattening partially depancreatized dogs. It is possible, and even likely, that the connection between

* Variations in diabetes incidence may, in part, be due to differences between populations in the distribution of the gene involved in the production of diabetes. It is not yet possible to estimate for any population how widely distributed this gene is.

obesity and diabetes is not a causal one and that both reflect some underlying imbalance in the functioning of the body, probably of endocrine origin. Despite this, however, the association of diabetes with a preceding obesity is so close that conditions favoring obesity are undoubtedly related to concomitant variations in the incidence of diabetes. Overweight as the exciting factor of the disease in susceptible individuals so much overshadows the other factors that the present discussion is largely devoted to it and the conditions favoring it.

Certain faults in the definition of obesity should also be noted. The usual standards, based upon arbitrary percentages above average weight, are, at best, approximations. Indeed, they lead to definite understatement of the degree and incidence of overweight. For, a characteristic of these standard tables is the increase of weight with age, a development which is neither inevitable nor physiologically sound. From the standpoint of mortality, the best weights—those which give the lowest mortality in adult life—are appreciably below the average.[10,11] They tend to correspond to the average weights of the late twenties or early thirties. If mortality is the best guide to what constitutes normal weight, our current standards are all too liberal. Another and possibly more fundamental objection is that these average weights leave out of consideration differences in bodily proportions, and the relative weights of the skeletal structure, muscle and fat. It may very well be that entirely different measures of obesity are needed. Suggestive in relation both to obesity and diabetes is the fact that the proportion of fatty tissue to total body weight is normally greater in women than in men throughout adult life. Significant differences also exist between persons of the same general build, but differing in musculature.

Environmental Factors and Their Relationship to Constitutional Factors. Most overweight results from overnutrition.[12] Even if, as previously suggested, a glandular disturbance is sometimes involved in obesity, it does not operate in the absence of overfeeding, absolute or relative. Whatever increases the chances of becoming overweight, therefore, will tend to bring about a real increase in the incidence of diabetes in susceptible overweights. Consequently, whenever and wherever conditions of life are easy, food abundant and relatively cheap over long periods, and when large numbers of individuals become accustomed to partake of food in excess of their requirements for the expenditure of energy, the frequent development of overweight and of diabetes is favored. These factors are also believed to underlie the differences in diabetes incidence in climatic areas demonstrated by Mills.[13]

Three broad groups of phenomena are involved in this theory, namely, mass variations in *per capita* energy requirements, food consumption and variations in the incidence of overweight. Data

only on the first of these are abundant and are presented in detail. In the case of the others, primary data are not available and we are forced to depend upon indirect evidence. For information on food consumption, we make use of certain indices, admittedly imperfect, such as income and purchasing power, because the facts on food consumption in the necessary detail do not exist. Moreover, because dietary habits have changed a great deal everywhere it is difficult even to determine whether food consumption on a caloric basis has really changed. In the United States it has apparently declined,[14] but not to a degree commensurate with the fall in *per capita* energy requirements. Facts on group variations in the frequency of overweight or on the increase in its incidence are also lacking. Because of the close association between diabetes and overweight, however, variations in the incidence of diabetes are presumed to correspond with variations in the incidence of obesity. For example, as we shall show in a later paper, Jewish diabetics are as frequently overweight as other patients. This indicates that the greater incidence of the disease in Jews must reflect a greater frequency of obesity. Probable evidence of increasing frequency of overweight is also indirect. It may only be inferred from insurance data on build, which show that there has been no decline in average weights among persons accepted for "Ordinary"* insurance,[15] although this type of insurance has been extended in large volume since 1919 to the working classes, among whom overweight is presumably less frequent than in the better situated classes.

THE SIGNIFICANCE OF CONDITIONS FAVORING OVERWEIGHT. (*a*) *Occupation and Social Status.* Our preceding paper[2] showed that rural death rates from diabetes are lower than urban rates. In rural communities, hard manual work is usual, particularly among farm laborers. The analysis of English occupational mortality, largely confirmed by recent American data,[16] showed that the incidence of diabetes among workers of this type was among the lowest recorded. Farmers and their families, however, who, on the average, do less work and are generally better fed and circumstanced, had a diabetes rate more than twice that of their laborers. In similar fashion, those engaged in coal mining, another type of work frequently involving hard manual labor and concentrated in rural districts, also had a very low mortality from diabetes. The high diabetes rates in cities, therefore, may be ascribed, in part, to the lighter work done by relatively large numbers of the urban population. Thus, our study of occupations showed high rates for persons engaged in professional callings and in clerical and mercantile pursuits, which usually require little actual labor. Yet, in these same urban areas, low rates are found among those doing hard manual work, for example, among laborers of all kinds.

* Insurance written in amounts of $1000 or more on an annual, semiannual, or quarterly basis.

Diabetes mortality of artisans, whose work usually requires a moderate amount of physical activity, is midway between that of the professional and laboring groups. Similarly, the differences in diabetes mortality between the various social classes, disclosed in our preceding paper reflect, to a great extent, merely the varying proportions of persons engaged in light and heavy work.

The high diabetes death rate among Jews may, in part, be due to the same causes. They have been for several generations an urban people. For a long time they were restricted to certain occupations and were not permitted to own land or till the soil. Relatively large numbers were engaged in the professions and in business. Despite the removal of earlier restrictions, succeeding generations have naturally followed the same sedentary occupations.

(*b*) *Regional Variations in Earnings.* As we have seen, the United States has the highest diabetes death rate in the world. Relatively high rates prevail in most of the British colonies. In Europe the rates in the northern countries are higher than those in the south and east, which means that they are higher among the Germanic groups than among the Latins and the Slavs. It is precisely in countries where diabetes is most frequent that the level of *per capita* income is high, and it is reasonable to assume that the level of nutrition corresponds with *per capita* income. The facts on comparative "real" earnings in the large cities (usually the capitals) of several countries, which are given in Table 3, are taken from the most careful study of the kind, made by the International Labour Office of the League of Nations.[17] International comparisons of this type are not altogether satisfactory because suitable standards are hard to devise, but the study quoted offers the most comparable data available.

It will be seen at once that the standards of living are reflected in the differences in diabetes mortality. Yet certain limitations of the data must be recognized. The groups considered were skilled and unskilled workmen in a few trades in which organization is often best and bargaining power highest. The proportion of unorganized semiskilled workmen and of industrial laborers was low. No consideration was given to agricultural laborers who, in many countries, constitute the largest group in the working population. The important mercantile and clerical groups were likewise excluded. To offset these deficiencies, however, it should be noted that the earnings of industrial, mercantile, clerical and agricultural groups stand roughly in the same relation to each other in all countries.

In the United States, also, regional variations in diabetes death rates tend to correspond with variations in income. Jordan,[18] taking the percentage of those filing income tax reports in the various states as an index of economic well-being, found that those states where the percentage was high usually had above average

rates from diabetes. *Per capita* realized income[19] in the several sections of this country also tends to correspond with the level of the diabetes death rates in the same areas. Table 4 shows that the diabetes rates are highest in the Middle Atlantic and New England states, where incomes are appreciably above the average, and lowest in the South, where the average income is low. The figures for the Mountain and Pacific regions are out of line. The income figures relate to the year 1919, but index figures for 1926, with 1919 taken as a base, show no material change in regional differences in income.[20]

TABLE 3.—STANDARD OF LIVING OF WORKERS IN VARIOUS COUNTRIES.

Number of Baskets of Provisions* Purchaseable with Wages as of October 1, 1926, based on the Average Wage for a 48-hour Week in Certain Industries, as Fixed by Collective Agreement. Base: London = 100.

City.	Index numbers of purchasing power of wages.			
	Several industries combined.†		Machinery manufacture—expert mechanics and machinists (no adjustment for rent).	Printing industry—hand compositors (no adjustment for rent).
	No adjustment for rent.	With adjustment for rent.		
Philadelphia	183	183	179[2]	125[2]
Ottawa	159	157	191	153
Sydney	137	137	163	109
Copenhagen	125	125	142[1]	97[1]
London	100	100	100	100
Amsterdam	96	96	112	84
Stockholm	92	90	..	73
Oslo	80	82	112[2]	90[2]
Berlin	69	63	84[4]	56
Paris	60[2]	61[2]	60	48
Madrid	56[3]	..	70[3]	56[3]
Warsaw‡	55	56	45	87
Prague	50	53	62	..
Rome§	46	48	55	40
Vienna	44	50	51	40
Brussels	44	47	59[2]	52[2]

* Separate indices were prepared based upon a series of typical food budgets for each of the following countries or groups of countries: Belgium and France, central European countries, Great Britain, southern European countries, Scandinavian countries, United States and British colonies. The figures presented are the averages of these separate indices.

† (*a*) Building trades: masons and laborers; (*b*) machinery manufacture: expert machinists and mechanics and laborers; (*c*) furniture manufacture: cabinet makers and laborers; (*d*) printing and bookbinding: hand and machine compositors and laborers.

‡ Wages are far higher than in other towns of Poland, particularly for the groups of workers studied.

§ Figures are relatively low because comparisons do not make adequate allowance for the high vegetable consumption in southern European countries.

[1] January 1, 1926; [2] April 1, 1926; [3] July 1, 1926; [4] October 1, 1924.

TABLE 4.—REGIONAL VARIATIONS IN INCOME AND DIABETES MORTALITY PER 100,000 IN THE UNITED STATES.

Per Capita Realized Income, 1919; Index of Income in 1926 (1919 = 100) and Standardized Death Rates from Diabetes, 1929–1931, Nine Census Regions.

Region.	Income.		Diabetes death rates.
	Per capita, 1919.	1926 index (1919 = 100).	
United States	$614	...	17.1
New England	715	114	17.9
Middle Atlantic	781	133	22.3
East North Central	669	121	17.8
West North Central	582	93	16.3*
South Atlantic	445	106	14.1
East South Central	345	107	11.4
West South Central	469	95	10.8†
Mountain	634	92	13.0
Pacific	793	120	14.2

* Excludes South Dakota.
† Excludes Texas.

TABLE 5.—REGIONAL VARIATIONS IN EARNINGS OF FACTORY WORKERS AND COMMON LABORERS AND DIABETES DEATH RATES IN THE UNITED STATES.

Estimated Annual Full Time and Actual Earnings of Factory Workers in 1923; Hourly Wage Rates of Common Laborers, January 1, 1928; and Total and Urban Diabetes Death Rates Per 100,000, 1928–1929.

Region	Factory workers, annual earnings.		Common laborers, hourly wage rates.	Diabetes death rates.	
	Full-time.	Estimated actual.		Total.	Urban.
United States	$1,545	$1,317	$0.43	18.9	24.4
New England	1,396	1,181	0.47	23.8	24.8
Middle Atlantic	1,774	1,501	0.49	24.5	27.4
East North Central	1,798	1,521	0.47	21.4	23.2
West North Central	1,511	1,278	0.41	20.1*	25.4*
South Atlantic	1,091	962	0.29	12.7	21.2
East South Central	1,111	980	0.27	10.6	21.1
West South Central	1,152	1,016	0.31	9.6†	19.2†
Mountain	1,661	1,556	0.44	13.8	21.6
Pacific	1,717	1,609	0.47	18.4	21.6

* Excludes South Dakota.
† Excludes Texas.

Similar regional relationships exist between the incomes of wage workers and diabetes rates. Table 5, which gives data on earnings of factory workers[21] and common laborers[22] in the 9 census areas, shows practically the same order as the preceding table. The averages given for factory workers relate to hypothetical full-time and actual earnings in 1923. The figures for the Mountain and

Pacific Coast states are much out of line with the diabetes death rates also shown in the table; but in both these areas, relatively few persons are engaged in factory work, and, moreover, in the Mountain states the average age of the population is low. The hourly wage rates of common laborers, as of January 1, 1928, show the same regional characteristics as factory wages, namely, relatively high rates in the Northeast and Pacific Coast states, average rates in the Middle West and low rates in the South. These regional death rates are crude rates. Consequently no allowance is made for differences in the proportion of older persons in the several regions. Unfortunately, necessary data are lacking to correct for this factor both in this and succeeding comparisons.

In agricultural regions, also, general agreement between diabetes incidence and income is found in the several parts of the United States. For this comparison, we are limited to rather old material, namely, Leven's estimate of *per capita* farm earnings in 1919–1921[23] (Table 6). Estimates of *per capita* income and income per farm family are given and, for comparison, diabetes death rates for rural areas are included. Again, high *per capita* income and high diabetes death rates appear to go together. To complete the picture, the earnings of agricultural laborers[24] (Table 6) also vary in the same way as the diabetes rates. These facts relate to prevailing rates of farm wages as of October 1, 1930. Later data are available, but are not used because the figures are abnormally low, although regional relationships are maintained.

TABLE 6.—REGIONAL VARIATIONS IN PER CAPITA FARM INCOME AND WAGE RATES AND IN RURAL DIABETES DEATH RATES IN THE UNITED STATES.

Per Capita Current Income (Excluding Value of Rent) of Farm Population and Income Per Farmer and Family, 1919–1921; Monthly and Daily Wage Rates for Farm Laborers, October 1, 1930, and Rural Death Rates Per 100,000 from Diabetes, 1928–1929.

Geographic division.	Income.		Wage rates.*		Rural diabetes death rates.
	Per capita farm population.	Per farmer (and family).	Monthly.	Daily.	
Continental United States	$282	$1,158	$44.28	$2.12	14.3
New England	437	1,355	64.65	3.27	21.5
Middle Atlantic	473	1,626			19.2
East North Central	337	1,289	50.14	2.60	19.3
West North Central	296	1,074			17.6†
South Atlantic	195	987	31.65	1.46	9.6
East South Central	159	740	31.23	1.40	8.2
West South Central	242	1,104			7.2‡
Mountain	446	1,653	73.97	3.14	11.0
Pacific	748	2,451			14.7

* Without Board. Wages with board vary in same proportions.
† Excludes South Dakota. ‡ Excludes Texas.

(c) *Extent of Industrialization and Urbanization.* The differences in the level of diabetes incidence in the various parts of the world, as well as within individual countries, also reflect the extent to which the inhabitants depend upon purely industrial, mercantile and professional pursuits, as opposed to farming and other activities requiring much physical labor. This phase of the problem is closely connected with the extent of urbanization, and it is impossible to disentangle the influence of each. Industrial and mercantile nations, which tend to be those having a large percentage of their populations in urban areas, usually show high *per capita* incomes and high diabetes rates. The factors of industrialization and high earnings really reinforce each other. Despite their lower *per capita* food requirements, workers in industrial and mercantile countries are able to buy as much food as those in countries where the greater

TABLE 7.—REGIONAL VARIATIONS IN OCCUPATION,* IN THE PERCENTAGE OF THE POPULATION LIVING IN URBAN† AREAS, AND IN THE DIABETES DEATH RATE.

Country.	Per cent in specified occupation groups			Per cent urban population.‡	Diabetes death rate per 100,000.§
	Agriculture and forestry.	Manufacturing and handicrafts.	Trade, transportation, communication and personal service.		
United States (1930)	22.0	28.9	30.5	56.2	19.4
New England	6.8	43.1	30.2	77.3	24.4
Middle Atlantic	5.4	36.3	34.0	77.7	25.5
East North Central	14.7	35.7	30.7	66.4	21.4
West North Central	33.8	19.9	29.9	41.8	20.6
South Atlantic	33.4	24.2	27.6	36.1	13.5
East South Central	48.3	16.9	23.1	28.1	11.0
West South Central	41.1	16.9	28.3	36.4	9.7
Mountain	31.7	18.3	29.1	39.4	13.3
Pacific	16.3	26.1	35.8	67.5	18.6
Canada (1931)	31.1	28.5	25.7	53.7	12.8
England (1921)	6.8	39.7	32.7	80.3	15.2
Belgium (1920)	19.1	39.9	23.3	60.5	15.9
Holland (1930)	20.6	37.2	30.9	78.8	17.6
Norway (1930)	35.3	25.9	32.1	28.5	11.6
Sweden (1920)	40.7	30.2	21.3	32.5	13.8
Denmark (1921)	34.8	27.0	30.0	43.9	17.9
Czechoslovakia (1930)	28.3	40.4	19.3	47.8	9.3
Italy (1931)	46.3	30.4	16.0	42.5	8.2
Australia (1921)	22.9	31.2	33.3	63.8	15.3
New Zealand (1926)	24.2	24.3	33.9	51.6	15.7

* In most countries, persons engaged in clerical work are assigned to the branch of industry to which they are attached. In the United States they are tabulated separately. In 1930 they accounted for 8.2% of gainfully employed persons.

† The definition of urban population differs from place to place. Usually it includes the population of incorporated cities and towns with a limit of 2000 or upwards. In Czechoslovakia, figures relate to communes of 2000 or over; and in Belgium and Holland, to communes of 5000 and over.

‡ Calculated for the same years as the occupational data, except Australia, 1933; England, 1931; Belgium, Sweden and Denmark, 1930; Italy, 1921.

§ 1932, except Belgium and Sweden, 1931; Italy, 1930; United States, 1929–1931.

number of inhabitants depend upon more arduous occupations for their livelihood. Consequently, one should expect a greater frequency of overweight and, therefore, of diabetes, in industrialized and urbanized communities. These tendencies are indicated in Table 7, which shows national differences and, for the United States, regional differences in diabetes mortality, in the proportion of persons in agricultural and two broad non-agricultural groups,[25,26] and in the proportion of the population living in urban areas.[27,28] The reader is cautioned, however, that there are certain differences in the classification, both of occupational groups and of urban populations; and on that account the figures given are general rather than absolute guides.

Evidences in Diabetes Trends of Conditions Favoring Overweight. The same forces which make for real differences in diabetes mortality between various countries and between areas within them are largely responsible for the upward trend of diabetes incidence and mortality. Most important of these are mechanization and the rising standards of living, which have been responsible for many profound changes in the structure of the modern world. These two not unrelated forces have acted in quite different ways to increase the incidence of diabetes by disturbing the metabolic equilibrium of large numbers of persons.

TABLE 8.—OCCUPATIONAL SHIFTS IN THE UNITED STATES, 1870–1930.
Per Cent of Gainfully Occupied Persons in Certain Broad Occupational Groups and in Certain Specific Occupations.

Occupation group.	1870.	1900.	1930.
Total	100.0	100.0	100.0
Agriculture and allied occupations	52.8	35.9	21.3
Mining	1.5	2.1	2.0
Manufacturing and mechanical industries	22.0	27.5	28.6
Trade and transportation	9.1	16.3	20.7
Total trade	..	9.6*	12.7
Sales people and clerks in stores	0.9†	3.0†	4.9
Clerical service	1.7	2.8	8.2
Domestic and personal service	9.6	10.0	11.3
Launderers, outside home	..	0.4*	0.5
Barbers and manicurists	0.2	0.5	0.8
Public service not elsewhere classified	0.6	1.0	1.4
Professional service	2.7	4.4	6.5

* 1910. † Estimated.

(*a*) *Occupational Changes.* The first important result of mechanization has been a flow of workers from more arduous occupations into jobs requiring less expenditure of energy. For the United States this is clearly brought out in Table 8, which shows the per cent distribution in 1870, 1900 and 1930 of gainfully occupied persons, 16 years of age and over, in certain broad occupational classi-

fications and for a few specific types of work.[29] In the interval of 60 years, between 1870 and 1930, the number of persons engaged in agricultural and allied occupations dropped from 52.8 to 21.3% of all occupied persons. Large absolute gains have been made in

TABLE 9.—CHANGES IN PROPORTIONS OF WORKERS ENGAGED IN AGRICULTURE, INDUSTRY AND TRADE IN SEVERAL COUNTRIES.

	Per cent.		
	Agriculture.	Manufacturing and mechanical trades.	Trade.
Australia:			
1921	22.9	31.2	15.3
1911	24.2	28.4	14.5
1901	†	26.1	13.6
Canada:*			
1931	31.2	...	12.2
1921	35.0	26.5	11.8
1901	42.6	28.0	9.0
England and Wales:*			
1921	6.8	39.7	13.9
1911	7.7	38.7	13.4
Great Britain:			
1911	8.5	18.4‡	...
1901	8.9	17.8‡	...
Belgium:			
1920	19.1	39.9	10.7
1910	22.5	40.4	11.9
Denmark			
1921	34.8	27.0	10.8
1911	41.7	24.2	10.4
France:*			
1926	38.3	31.2	11.5
1921	41.5	28.4	10.4
1906	42.7	28.8	9.7
Germany:			
1925	30.5	41.4	16.5
1907	34.0	39.1	13.9
1895	36.4	37.7	10.9
Netherlands:			
1930	20.6	37.2	14.0
1920	23.6	36.1	11.7
1909	28.4	34.2	10.8
Norway:			
1930	35.3	26.5	12.5
1920	36.8	27.4	11.1
1910	39.5	25.1	8.8
Sweden:*			
1920	40.7	30.2	8.4
1910	46.3	25.1	5.4
Switzerland:			
1930	21.3	44.6	14.6
1920	26.6	44.7	11.7
1900	32.2	46.1	9.3

* Includes all persons connected with each branch of industry. In all other cases the classification is according to occupation.

† Primary producers (farmers and their laborers, cattlemen, miners, etc.) 1900, 32.5%; 1911, 30.4%; 1921, 25.8%.

‡ Selected manufactures.

the percentage employed in factories, but by far the greatest gains, absolutely and relatively, are recorded for trade and transportation, clerical work, professional and semiprofessional occupations and public employment. In the trade and transportation groups, much the largest gain has been made by the trade group. The number of persons engaged in domestic and personal service, as a whole, has shown a very slight upward trend, but the increase seems to be concentrated in personal service, especially among such workers as waiters and other restaurant employees, barbers, hairdressers, manicurists and launderers working outside the home.

Similar occupational changes are noted in most other countries.[25] Since the World War, these changes have been accelerated by the policies of economic nationalism, especially in the European countries set up after the conflict. The extent of this is not fully demonstrable because of the lack of sufficiently detailed or up-to-date statistics and because of boundary changes. Despite these difficulties, the world-wide trend from agricultural to manufacturing pursuits, clerical and professional work and certain types of personal service is evident in Table 9.

(*b*) *Increased Use of Power.* Coincident with this change in the occupational pattern, there has been a drastic reduction in the amount of human labor through the use of power-driven machinery. The extent of the change in the United States is shown by comparing the changes in the number of wage earners engaged in manufacturing and in the rated horsepower capacity of plant equipment.[30] The increase in power-driven equipment has far outstripped that in the number of wage earners. In the 30-year period, 1899 to 1929, the number of wage earners increased only 88%, compared with an increase of 331% in power equipment capacity. In the decade between 1919 and 1929, despite a slight decrease in the number of wage earners, the power capacity increased nearly 50%. The horsepower per worker rose from 2.1 in 1899 to 3.3 in 1919 and 4.9 in 1929.

This development is not limited to the manufacturing industries alone. There has likewise been a rapid expansion of the use of machines driven by mechanical power in other types of work, in mining, in officework, on the farm and even in the home. Exemplifying the change in the farm picture is the enormous growth in the use of tractors in this country from only 80,000 in 1918 to 447,000 in 1923 and 853,000 in 1929, the last year for which the figures are available.[31] Thus, in the short period of 11 years the number of tractors in use increased over $10\frac{1}{2}$ times, while the number of farmers and their laborers changed little.

The increase in labor-saving devices in the home is indicated by the rapid increase in the domestic consumption of electricity.[32,33] In 1913, the first year for which figures are available on a national scale, the domestic consumption of electricity was 1,025 million

kw. hrs. By 1923, the consumption had increased to 4,300 millions; in the succeeding 9 years, to 11,987 millions. In the 19 years, between 1913 and 1932, domestic consumption of electricity increased elevenfold, while the population rose about 30%. Much of this increase in domestic electrical consumption is, of course, accounted for by home lighting, but no small part of it is attributable to use of domestic labor-saving devices, which have increased steadily in recent years.[34] In connection with the reduction in domestic labor, mention should be made of the increased use of gas and electricity for cooking purposes in place of the old-fashioned coal stove, and also of oil and gas for domestic heating in place of coal furnaces.

The replacement of human labor by power-driven machinery is a characteristic development of our times. It is found in every country. Its extent varies from place to place, although it is difficult, if not impossible, to measure these differences. A sufficient indication is the increase in the output of electrical power in several countries between 1925 and 1931 (Table 10).[35]

TABLE 10.—INCREASE IN OUTPUT OF ELECTRIC POWER IN PRINCIPAL COUNTRIES OF THE WORLD, 1925 TO 1931.

Country.	Output of electric current* (millions of kilowatt-hours).	
	1925.	1931.
United States	73,791	91,700
Canada	10,480	16,383
Belgium	3,214	3,851†
Denmark	223	501‡
France	9,700	13,974
Germany	11,521	25,260
Italy	7,600	10,603
Netherlands	896	1,878
Norway	4,200	10,500‡
Poland	1,300	2,865§
Sweden	3,500	4,982‡
Switzerland	4,190	5,707†
United Kingdom	8,320	11,401
Japan	6,400	13,780§

* In most cases figures cover central stations only, not isolated plants.
† Estimated. ‡ 1929. § 1930.

(c) *Increase in "Real" Incomes.* The development of modern machine industry has brought about a large increase in the productivity of the workers. In the United States,[36] if 1899 is taken as a base, the index for physical volume of production in 1929 was 310 for manufactures, 338 for transportation (railroad ton miles) and 386 for mining, whereas the index of population was only 162. Agriculture failed slightly to keep pace, its index of production reaching 148, but this is partly offset by a decline in the exportable

surplus. The result of this greater productivity has been an increase in the "real" incomes of the masses, both in this country and abroad. This has, of course, not been an uninterrupted development. The length and severity of the depression, which began in 1929, have in some quarters aroused the fear that there is to be an extended recession in living standards of the masses. It is probably a saner judgment, however, that this depression, like earlier ones, will prove no more than a temporary and cyclical one and that the upward trend in industrial production and the consequent improvement in living standards will be resumed. A definite increase in the "real" incomes over and above changes in price levels took place during the two decades preceding 1928. This is brought out clearly in Table 11, which gives Douglas' indices of real earnings of persons in all types of work and in the principal industrial groups[37,38] and Brissenden's indices of earnings for all factory workers.[39] To eliminate cyclical variations, 3-year averages are used. It will be noted that the increase in "real" incomes has not been concentrated in favored groups, but extends to every branch of activity. Although the increase varies from one industry to another, it is distinct in each of them.

TABLE 11.—TREND OF REAL EARNINGS IN THE UNITED STATES, 1899 TO 1928.

Index Numbers of Annual Earnings, Adjusted for Changes in Price Levels, of All Workers and Workers in Certain Manufacturing and Other Industries. (Estimates by Douglas except as noted.) 1914 = 100.

Period.	All workers.	Manufacturing industries.											
		All factory workers* (Brissenden).	All factory workers.	Food.	Textile.	Clothing.	Iron and steel.	Lumber.	Paper and printing.	Land vehicles.	Public utilities.	Coal mining.	Clerical work.
1899–1901	93	104	100	101‡	102	101	100	99	97	86	96	...	106
1904–1906	96	109	101	100§	99	104	99	103	98	89	93	111	104
1909–1911	98	105	101	102	99	104	99	90	97	97	95	108	102
1914–1916	103	111	102	102	104	104	102	102	101	107	102	111	101
1919–1921	109	116	114	111	119	116	114	106	106	110	109	121	88
1924–1926	124	141	128	124	129	129	128	118	135	126	117	133	104
1928	132	140†	...	128	131	135	134	123	144	138	122	133	114

* With allowance for unemployment and overtime. † 1927. ‡ 1899. § 1904.

Similar changes in incomes and presumably in standards of living are noted in other countries as well. The most adequate study of this type was made by the International Labour Office of the League of Nations,[40] but unfortunately closes in 1925, when some countries had not yet recovered from the effects of post-war inflation of currencies or other financial or economic difficulties. Examination of Table 12, which gives a comparison of "real" wages in 1913–1914 and 1925 for workers in several countries reveals a distinct improve-

ment in workers' earnings in most of them. Countries in which there was little or no depreciation of currency have been segregated from the rest. In general, the improvement in incomes has been greater in them than in other countries. It is most significant, too, that in general the position of the poorer paid workers, the unskilled, has shown greater improvement than that of skilled workers. Prior to 1914, also, it is believed, "real" incomes of workers were improving in most countries.

TABLE 12.—REAL WAGES IN VARIOUS COUNTRIES IN 1925 COMPARED WITH PRE-WAR WAGES.

Index Numbers of Real Wages for Two Groups of Countries: Those With Little or No Post-war Depreciation of Currency (Group A) and Those With Large Depreciation of Currency (Group B). (1913–1914 = 100.)

Country.	Metal and engineering trades.		Building trades.		Printing trades.		Textile trades.		Mining.	
	Skilled.	Unskilled.	Skilled (carpenters).	Unskilled.	Skilled (compositors).	Unskilled.	Skilled.	Unskilled.	Skilled.	Unskilled.
GROUP A:										
United States	116[3]*		113[6]	116[6]	120[3]*		135[3,8]*			
Canada[1]	120*		116		131[7]				132	
Australia	117*		109*		116*				109*	
New Zealand[1]	90		93	90			104			
Great Britain	84	102	105[6]	119[6]	120		118[8]*		89*	
Switzerland[2]	127		120[6]	121[6]						
Netherlands					135[2]		122[2]		105	
Sweden	120*		125	139	130*		103*			
Norway[1]	111*		95	97						
Denmark	129	125	124	143	107	114	131			
GROUP B:										
France	109[5]		123[5,6]	126[5,6]	126[5,4]		131[3]*		101*	
Germany	86	91	94	101	86	91	83	81	94	
Austria	108	120	150	164	103[7]		98			
Poland	69[5]	83[5]	89[4,6]	144[4,6]	181		66[5]			
Czechoslovakia	87	81	86[4]	87[4]	99					

(No data available.)

[1] 1924. [2] 1923. [3] New York. [4] Capital city.
[5] Lodz. [6] Bricklayers. [7] Total. [8] Average cotton and wool workers.
* Skilled and unskilled combined.

To a certain extent the movement of "real" wages understates the improvement in living standards. In the first place, the size of workingmen's families has fallen as fast as in other sections of the population, and, consequently, there are, on the average, fewer persons to provide for with the wages earned. In the second place, average wages do not completely reveal the family income. The more frequent employment of women in industry, especially of married women, has increased family earnings to a far greater extent than the changes in *per capita* earnings would indicate.

There are, moreover, important additions to "real" income through the increased amount of free services supplied by the state or by private philanthropies. Certain factors, in part, offset these hidden additions to income, as, for example, the greater proportion of income which must be spent on rent in growing industrial areas.

(*d*) *Increased Leisure.* Another byproduct of our mechanized civilization is the increasing amount of leisure. Not only do men work less hard during their occupied hours, but they have more free hours. Fifty years ago, the 60-hour week was general in the United States, Germany, France and Belgium, a 52-hour week in England, but 72 hours in Italy, Russia and other countries. Even longer hours of work were not uncommon.[41] Since 1890, there has been a marked reduction in hours of labor. There are no comprehensive statistical data on the subject, but there is enough material to show the trend In the United States, Douglas estimates the average working hours in certain trades at 58.4 in 1890, 57.3 in 1900 and 53.8 in 1913. A survey by the National Industrial Conference Board shows a decline for manufacturing industries from 55 hours in 1914 to 49.6 in 1927. Just before the World War, in many countries the 8-hour day already had obtained a strong foothold, especially in unionized industries. After the World War, the 8-hour day became even more general, expedited by international agreement. By 1928, a working week of 48 hours or less was enjoyed by more than 80% of full-time workers in England, Austria, Belgium, Czechoslovakia, Denmark, Holland and Sweden. In highly unionized industries the 44-hour week or less has become general, and in practically all, the working week is not more than 48 hours. This downward trend in the hours of labor will probably continue for a while. For example, a week of 40 hours or less is specified in most of the industrial codes of the NRA.

Education of the working classes in the proper use of leisure time has been woefully neglected, and even in the upper classes it is most inadequate. The result of the poor training and facilities for leisure is described in vivid, if exaggerated, terms by Nystrom:[42] "There is also the dangerous tendency with increasing leisure for individuals to become fat and flabby in mind as well as in body. The critics of leisure point to the menace of declining energy, ambition and ability among those whose leisure time is increased. This flabbiness and laziness is evident in both sexes, and may be seen in the growing tendency to ride instead of to walk, to participate in sports as spectators rather than as players and to shirk responsibility and effort in every form."

(*e*) *Increasing Urbanization.* Another aspect of our changing civilization, significant in relation to the increase in diabetes, is the growing concentration of population in cities, that has been fostered or imposed by the development of our present industrial organization. The trend toward the cities has resulted in cutting

down the expenditure of energy of large numbers of individuals. For example, the recreational activities of city dwellers tend to the passive types. For women, the removal to the city brings about a change to easier work, inherent in the differences between the city and country household. Again, transportation facilities and their use are much greater among urban residents. Differences in occupational patterns of the city and country need not be considered here because they have already been given their due weight. Moreover, the greater availability of concentrated foods, rich in calories, undoubtedly encourages overnutrition among urban residents. Urbanization, then, is a factor in the real increase in diabetes, and facts on the extent of this change are important.

In the United States, only 30 years ago, 60% of our people lived in the country, but today we are an urban people with only 44% of our population in rural areas. In the space of a generation the population of our cities has increased 125%, but our rural population has grown less than 20%. Moreover, the actual farm population in the country decreased in the decade 1920 to 1930. The increase in the rural population during the decade was limited to those residing in country villages. Because of the depression, many urban residents returned to their former homes in the country after 1930. Estimates of this movement run as high as 2,000,000 persons. This is, however, a purely temporary phenomenon and there is already evidence that the movement has again been reversed.[43]

TABLE 13.—GROWTH IN PROPORTION OF URBAN RESIDENTS* IN PRINCIPAL COUNTRIES, 1900–1930.†

Country.	Per cent residing in urban areas.	
	1900.	1930.
United States	40.0	56.2
Belgium	52.3	60.5
Canada	37.5	53.7
Denmark	39.1	43.9
England and Wales	77.0	80.3
Finland	12.5	18.2
France	40.9	49.1
Germany	43.8	53.6
Netherlands	70.3	78.8
New Zealand	39.1	51.6
Norway	28.0	28.5
Union of South Africa	52.9	61.3

* Definition of "urban" is not the same for all countries, although for each country comparable populations as of the two dates are used. In most cases, incorporated cities and towns are included; sometimes with a limitation as to size. In Belgium, Netherlands and Germany, communes over a certain size are included.

† Census data closest to these years. Most of the dates fall within 1 year. Exceptions are: 1930, France and New Zealand (1926), and Germany (1925); 1900, Union of South Africa (1904) and Netherlands (1909).

The long-time movement to the city is by no means limited to the United States. As Table 13 shows, cities throughout the world, almost without exception, have been growing faster than the country, and to a great extent at its expense. Generally speaking, this trend is greatest in the countries, particularly the British commonwealths, which have been developed latest. In England itself the change has been very small, but in this case the rural population had already diminished to about one-fifth of the total population three decades ago.

(*f*) *The Position of Women.* The greatly increased incidence of diabetes in women reflects to a great extent the gradual improvement in their position in modern times. This development is intimately related to the broad social changes already described, but the interest in it at this point is to review the effect on the actual physical work done by women. This has become progressively less in modern times, especially in industrial communities. Lower birth rates, which are a characteristic development all over the world, mean fewer children to work and care for. Smaller homes, epitomized by the small apartments of large cities, also have the effect of lessening work. Moreover, many of the former functions of the housewife—cooking, baking, food preserving, laundering and the making of clothing—are now largely carried on in industry. Whatever work remains in the home is rendered easier, as we have seen, by new domestic labor-saving devices. These are widely used in farm as well as in city homes. Another important development has been the great reduction in the number of domestic servants. Women who are dependent on their own earnings have come to prefer jobs in factories and offices, where work is easier, normally better paid and the hours are shorter. The effect of all these changes is, of course, not immediate, and none of them has yet exercised its maximum influence. For example, the decline in birth rates has been most rapid in recent years, and the women of childbearing ages of those years are only now approaching the "diabetes age."

The Recognition of Diabetes.

The Influence of Medical Facilities on Its Differential Incidence. The factors thus far discussed are those which make for real variations in the incidence of diabetes. Not all cases of the disease, however, are diagnosed, and the reported incidence must likewise be considered. In this, the extent and quality of medical services are the major items but, as indicated in the second paper,[5] differences in official statistical procedures in classifying deaths also play a part. In general, countries economically well off have better developed medical services than those less favorably situated, although this will not be uniformly true. Within all countries and regions, of course, the more prosperous classes have freer access to the best

medical facilities and make more frequent use of them than the lower economic and social groups. The chances of correct diagnosis of diabetes are then generally better for wealthier nations and classes.

Comparative data on the proportion of physicians and of beds in general hospitals to population in various countries and for several regions of the United States, presented in Table 14,[44,45] show that the diabetes rates are generally high in areas which have the greater number of physicians and hospital beds, and are low where the medical facilities are poorer. The correspondence is best in respect to hospital beds. Complete correspondence is not possible because of such factors as the differences in the quality, training and equipment of physicians in various areas, the development of socialized medicine in certain countries and the growth of specialized hospitals. In certain countries, furthermore, highly developed medical centers attract large numbers of foreign patients, Vienna being the prime example.

TABLE 14.—PHYSICIANS AND GENERAL HOSPITAL FACILITIES IN THE UNITED STASTE AND ITS SUBDIVISIONS AND IN SEVERAL FOREIGN COUNTRIES.

Number of Physicians and of Beds in General Hospitals Per 10,000 Population.

Country.	Physicians per 10,000 population, 1929.	Beds per 10,000 population, 1928.
United States	12.6§	37.0
New England	13.6	50.5
Middle Atlantic	13.6	
East North Central	12.8	37.5
West North Central	13.1	
South Atlantic	10.8	23.3
East South Central	10.6	19.7
West South Central	10.9	
Mountain	10.8	47.8
Pacific	17.3	
Great Britain	12.2	
Austria	12.0‡	43.0
New Zealand	9.1§	45.5
Switzerland	8.4*	46.5
Denmark	7.6	49.9
Germany	7.4	59.0
Belgium	6.8	29.4§
France	6.6	
Czechoslovakia	6.5	24.3†
Norway	6.1‡	39.2
Netherlands	5.6‡	32.0†
Sweden	3.8	25.4
Poland	3.1‡	2.1†

* 1930. †1929. ‡ 1928. § 1927.

Urban and rural variations in the incidence of diabetes may likewise reflect, in part, differences in the medical facilities avail-

able. Everywhere physicians tend to congregate in the larger and more prosperous cities. There is constant complaint of the dearth of physicians not only in the country but even in the small towns outside the metropolitan zones. To some extent the situation today is better than appears on the surface, because modern transportation enables the small town and rural residents to avail themselves of urban medical services. At the same time physicians, both in town and country, serve a much wider area than formerly. Only in sparsely settled sections is the situation really bad.

The Influence of Medical Progress on the Increase in Diabetes. In like manner, developments in the field of medical service have tended to increase the number of recognized cases everywhere. In this connection, one must bear in mind that these improved medical services have become available to an increasing proportion of persons as a result of the concentration of populations in urban areas and because of improvement in transportation. In this country, the important change in the medical field is not an increase in the number but in the quality of physicians. The proportion of physicians to population has steadily dropped from 17.3 per 10,000 in 1900 to 12.6 in 1927.[45] This tendency is found in almost every section of the country. In most foreign countries, on the other hand, the proportional number of physicians has been growing.[46] (Table 15.) But everywhere there has been increasing emphasis on the quality of the candidates admitted to study and great improvement in the standards of medical education.

TABLE 15.—CHANGE IN THE RATIO OF PHYSICIANS TO POPULATION IN CERTAIN COUNTRIES, 1900–1925.*

Country.	Physicians per 10,000 population.	
	1900.	1925.
Germany	4.6	6.9
France	4.9	5.9
Belgium	5.3	6.2
Netherlands	4.5	5.5
Sweden	2.2	3.2
Norway	5.0	5.5
Switzerland	6.7	8.1
England and Wales	7.0	6.4
Canada	10.2	10.6

* Data are those available closest to these years. Most of the dates fall within 2 years. Exceptions are: For 1900, France (1906) and Switzerland (1910); for 1925, England and Wales and Canada (1921) and Switzerland (1928).

Changes in the quality of the medical personnel are not measurable, but there are other significant statistical evidences of improvement in medical care. For example, in the 30 years between 1900 and 1930 the number of hospitals in the United States increased

from 2070 to over 6500* and the number of hospital beds even more.[47,48] This increase in hospital facilities extended to every type. The number of beds per 10,000 population in general hospitals rose from 25.8 in 1925 to 31.3 in 1932. There was a negligible decline in 1933. The *per capita* expenditure of cities of 30,000 and over for these hospitals increased over 3 times between 1913 and 1928 and 5 times between 1903 and 1928.[49] The number of general hospitals with outpatient departments rose from 703 in 1921 to 1562 in 1931, and every section of the country benefited from this increase. The number of clinics of all types grew from about 150 in 1900 to 3944 in 1921 and 7595 in 1931.[50] The extent to which all these clinics are used is not available, but the number of visits reported in 24 of the 25 largest cities of the country increased from 7 millions in 1921 to nearly 14 millions in 1931. Between 1927 and 1931 alone, there was an increase in the number of visits to outpatient departments in this country from nearly 14 millions to 23.5 millions. Finally, there has been a rapid growth in the number of private clinical laboratories.

Similar expansion of hospital facilities has been going on in many countries. No systematic collection of data on this matter exists, but the facts for a few countries clearly show the trend. In Germany, for example, the number of beds in general hospitals rose from 29 per 10,000 population in 1900 to 55 in 1926, and in Sweden, from 21.6 in 1900 to 39.6 in 1926. In France, the number of hospitals increased 15.1% and the number of persons treated 74.3% between 1900 and 1930, while the population showed an increase of only 6.4%. In Switzerland, the number of hospitals increased 51% between 1916 and 1930 and the number of admissions 55%, while the population increased only 6.2%.

The growth of industrial medical services has also favored more frequent diagnosis of diabetes in recent years. In 1930–1931, 5564 plants, with 4,200,000 employees, were known to provide some form of medical service.[51] More than one-half these plants, employing 3,100,000, required medical examination prior to employment, and periodically thereafter. These examinations often include an urinalysis and, when necessary, a blood sugar estimation. Consequently, an increased number of diabetics has been discovered in this manner. Moreover, many modern plants do not limit their medical services to examinations or first aid. At the time of the survey just quoted, 773 industrial plants employed 617 full-time physicians and 518 on part time for the medical care of their employees, numbering about 600,000. In no less than 515 plants with 430,000 employees, medical care was extended to the workers' families.

* In recent years the number of hospitals has been declining, but this is partly due to amalgamation of previously existing units. The number of hospital beds has continued to increase.

Another development which has increased the chance of a correct diagnosis of diabetes is the growing frequency of medical examination of supposedly healthy persons. The most important factor in this situation in the United States is the vast growth of life insurance in recent decades, examinations for which have long included a routine urinalysis. Distinct advances have been made in the technique and its standardization in the large biochemical laboratories of the life insurance companies. In recent years the number of blood sugar estimations for life insurance examination has also been growing rapidly. This trend will be accelerated by the method, developed 3 years ago, of preserving small samples of blood so that blood sugar estimations of samples taken by medical examiners in the field can be made by a standard technique at home office laboratories. The importance of life insurance in this matter in the United States may be realized from the number of persons applying for life insurance requiring medical examination, which has reached the figure of 4 millions in some recent years and even today is about 3 millions per year. More direct evidence of the place of life insurance in the identification of diabetes is that 15.9% of all Joslin's male patients of insurable age were discovered in this manner and, of the cases seen between 1920 and 1928, actually 17.7%. In view of the particularly sharp advance in the incidence of diabetes in women, it is significant that the number of women applying for life insurance has been increasing at a much faster rate than of men. For example, in 1900 women constituted, only 7.6% of all "Ordinary" applicants in the Metropolitan Life Insurance Company, but in 1930 the proportion was 26.9%. In these 30 years, which witnessed a tremendous growth in life insurance, female applicants in the Company increased by over 80 times, while male applicants increased by about 20 times. That life insurance is a factor in the increased recognition of diabetes in many other countries also may be inferred from the growth in the *per capita* amount of insurance in force, especially during the past decade.[52]

Similar in its nature and significance is the growing popularity of periodic health examinations. Life insurance companies have done much to foster this development, even to the extent of paying for the examination of their policyholders. That this is not a matter of slight importance may be realized from the fact that over 100,000 policyholders of the Metropolitan Life Insurance Company alone took advantage of this service in 1933. Since 1920, their number has grown tenfold. The number of individuals receiving periodic examinations from their personal physicians must also be very large today, due to the persistent efforts of medical societies to popularize the idea of periodic physical examination.

Certain other advances in the field of medicine, even if their effects are as yet not measurable, are nevertheless significant in regard to diabetes. On the one hand, there have been distinct

advances in the techniques involved in the diagnosis of diabetes. While tests for urinary glycosuria are not new, the methods in use at the present time are of relatively recent origin. This is even more true of cheap and accurate tests for blood sugar, particularly of micro methods. Moreover, routine examination, even of urines for sugar, is relatively recent. Bolduan[53] has shown that even in a high-grade institution like New York Hospital, this did not become the practice until some time between 1880 and 1890. Routine blood sugar estimation has not been done in many hospitals for more than a few years, and even today is not widely done. The increased use of diagnostic aids is also in part the result of changes in the training and personnel of the medical profession. The passing years have brought in a new type of physician, trained from the beginning in the use of modern diagnostic techniques and thus accustomed to use them more freely than the older generation of physicians.

These advances are not limited to any one country. The wide and rapid diffusion of scientific knowledge makes new techniques available within a relatively short time to physicians in all parts of the civilized world. Modern industrial methods make possible the manufacture of new equipment at prices which soon bring it within the reach of hospital groups and physicians everywhere. Modern methods of organization promote frequent use of these facilities, thus bringing down the unit costs to relatively modest figures.

These changes in the medical field have come about during an era in which there has also developed a new and franker attitude toward the body and its functions. This has been especially true in regard to women. For this reason greater attention has been directed toward their medical needs, and the medical services rendered to them have increased. This also has aided in the discovery of more cases of diabetes.

Other Factors in the Increasing Incidence of Diabetes. An apparent increase in diabetes has resulted from the steady growth in the proportion of old persons in the population and especially of older women,* among whom diabetes is most frequent. Increase from this source is viewed as apparent because it occurs without any change in the specific age and sex rates of incidence of diabetes. Table 16 shows that the growth in the proportion of older persons is characteristic of almost all civilized countries.[54,55] In the United States, for example, the number of persons aged 45 and over constituted 22.8% of our population in 1930, compared with only 18.9% in 1910 and 17.7% at the beginning of the century. Stated in another way, the number of people in the United States at ages past 45 has

* In our discussion of diabetes death rates, the effect of these factors was discounted in comparisons of rates adjusted for changes in sex and age—not, however, in crude death rates which were of necessity more frequently used.

more than doubled in the last 30 years, while the total population has grown by only 62%. The increase in the number of older women is even greater.

TABLE 16.—THE INCREASING PROPORTION OF OLDER PERSONS AND OF OLDER WOMEN IN THE POPULATION OF PRINCIPAL COUNTRIES, 1900–1930.*

Country.	Percentage of population.					
	Persons.				Females.	
	Ages 40 and over.		Ages 60 and over.		Ages 40 and over.	
	1900.	1930.	1900.	1930.	1900.	1930.
United States	23.4	29.4	6.4	8.5	11.1	14.2
Australia	21.9	31.1	6.2	9.4	9.5	15.3
Belgium	27.9	33.2	9.5	10.3	14.4	17.1
Canada	24.5	28.5	7.7	8.4	11.7	13.2
Denmark	28.4	31.7	9.8	10.8	15.0	16.6
England and Wales	25.3	35.7	7.4	11.4	13.4	19.3
Finland	26.9	30.3	8.2	9.4	14.2	16.1
France	35.1	38.5	12.5	13.8	18.2	20.6
Germany	25.7	33.3	7.8	10.4	13.6	17.7
Ireland	29.0	33.3	10.9	12.3	15.0	16.7
Italy	29.1	30.3	9.6	10.8	14.8	15.9
Netherlands	26.8	29.1	9.2	9.4	13.8	14.9
New Zealand	22.7	31.9	6.7	8.7	9.5	15.4
Norway	28.4	30.8	10.8	11.6	15.3	16.6
Spain†	28.2	29.1	8.2	9.5	14.0	15.3
Union of South Africa‡	17.0	26.0	3.4	7.1	7.1	12.3

* Data relate to censuses closest to these years. Most of the dates fall within 1 year. Exceptions are, for 1930, Ireland and France (1926) and Belgium and Spain (1920); for 1900, Union of South Africa (1904).

† Ages 41 and over and 61 and over. ‡ European population.

A real increase in the number of diabetics in recent years has also come about as a result of the prolongation of life of diabetic patients, chiefly through the use of insulin. In a later paper, we shall show how great has been the actual reduction in the death rate of diabetics, which is, of course, quite a different thing from the death rate from diabetes in the general population. The net result of the recent advances in therapy has been to increase the number of diabetics living at every age, but most of all at the younger ages.

While we do not lay much stress on racial susceptibility, a possible factor in the increased frequency of diabetes in some areas is the rapid growth of race stocks with a higher than average incidence of diabetes. Thus, the number of Jews in the United States has increased nearly fourfold in a generation—from slightly more than 1 million in 1900 to over 4 millions at the present time.[56] For the

country as a whole, the item is not a large one. Jews constituted 1.3% of our population at the beginning of the century and even today, only 3.2%. This influence is much more important in a city like New York, where the number of Jews has risen in the past 30 years from 600,000 to over 2 millions.[57] Moreover, the growth resulted largely from immigration of young people who are only now beginning to be represented in large numbers in those older age groups where the mortality from diabetes is highest. The Jews are singled out for specific mention because of the interest in their high incidence of diabetes. The same thing applies in lesser degree to some other racial groups. This factor, if at all important, is significant only in countries which have been growing by immigration, but not in the more settled countries.

Summary and Conclusions. Overweight is the most common factor in the etiology of diabetes. The evidence shows that variations in diabetes mortality, whether from the point of view of regional or social distribution, or from the point of view of changes in time, are associated with environmental conditions which influence the frequency of overweight. Thus, diabetes is found to be most prevalent among persons whose work requires the expenditure of relatively little physical energy and who have higher than average incomes. Likewise, the disease tends to be most frequent in societies in which "real" incomes, as measured by purchasing power of wages, are highest and the proportion of persons engaged in light work is greatest. These basic conditions also explain the real increase in diabetes throughout the world. The rapid expansion of the use of machines driven by mechanical power has made industrial workers mere tenders of machines, has lightened the burden of farm workers, transferred large numbers into clerical and sales jobs and reduced hours of labor. The amount of energy expended in work, therefore, has been drastically cut down for the majority of the working population. The growth of urban areas, often at the expense of the country, has made ever larger numbers subject to these influences. Concomitant with these developments, if not as a result of them, an increase in "real" wages has occurred. Consequently, at the same time that individuals have been called upon to work less hard, thus reducing food requirements, they have become able to buy more food. Either condition alone would favor an increased frequency of overweight and, therefore, of diabetes. Together their power is greatly enhanced to bring about the pathology we call diabetes.

As for women, the very great increase in diabetes among them reflects the betterment in their social position. They have shared in the benefits of the increasing family income. Domestic labor has been lightened by the decreased size of the family, by the transfer of many domestic functions to industry and by the use of

labor-saving devices in the home. Moreover, employed women have tended to drift into less arduous jobs. Increasing attention to the medical needs of women has also undoubtedly resulted in the more frequent recognition of diabetes among them.

Another factor in the differential incidence of diabetes is the quality and efficiency of medical service. Diabetes rates are generally highest where either medical facilities, as measured by hospital beds to population, are most abundant, or physicians in proportion to population, most numerous. More frequent discovery of the disease, causing an apparent increase in its incidence, has followed an increase in medical facilities, widespread improvement in medical education and important advances in diagnostic methods. These methods have become increasingly familiar to the average physician, largely as a result of the gradual replacement of the older members of the profession by younger men trained from the beginning in these newer techniques. At the same time, these procedures have been used on a vastly increased scale as a result of their routine use in hospitals and the medical examination of large numbers of supposedly healthy persons for insurance and health purposes. Modern medical service has become available to an ever increasing proportion of the population as a result of the concentration of populations in urban areas.

The rise in the incidence of diabetes also reflects the great change in the constitution of populations. Everywhere the proportion of persons in middle and later life, among whom diabetes is most frequent, has been steadily increasing. Especially is this true of older women. Another factor, significant in certain areas, is the differential increase of race stocks which seem to be especially susceptible to the disease. A third item not to be overlooked is that the improvement in diabetes therapy, largely as a result of insulin, has itself increased the number of diabetics living.

The increase in the incidence of diabetes is only in part a real one. Such is the increase resulting from environmental changes which favor frequent overnutrition and also that following the reduction in the mortality of diabetics due to insulin. On the other hand, the increase in diabetes due to the growing proportion of older persons is not a problem to give concern, because the sex and age characteristics of the disease make it inevitable. The rest of the apparent increase in diabetes incidence results largely from the identification of cases which formerly escaped attention. Not one new case of the disease is added to the true number by improvement and more frequent use of medical facilities. The question naturally arises as to the relative importance of the several factors mentioned —how much of the increase in diabetes is real, and how much apparent. In the present state of our knowledge, however, it is impossible to give a definite answer to this question.

It is likely that the incidence of diabetes will continue to grow and diabetes death rates likewise to increase moderately for several years, until the forces described in this paper reach equilibrium. Advances in industrial technology are still being made. Consequently, the productivity of workers may be expected to increase; mechanical power to displace human labor to a greater extent than today, both in industry and agriculture; and standards of living to rise. As a result, a further real increase in diabetes will occur unless we are more successful than we have been in educating the public as to the dangers of overweight and how it may be prevented. Some further growth in the number of diabetics may be expected as a result of further increase in the average age of the population, which will not become stationary for several decades. The recognition of the disease will also be more frequent in the future because of improvements, still being made, in the efficient use of our medical resources and in diagnostic techniques.

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THE ACTION OF THEVETIN, A CARDIAC GLUCOSID, AND ITS CLINICAL APPLICATION.*

By Harry L. Arnold, A.B., M.D.,
MEDICAL STAFF, QUEEN'S HOSPITAL,
HONOLULU, T. H.,

William S. Middleton, M.D.,
PROFESSOR OF MEDICINE, UNIVERSITY OF WISCONSIN MEDICAL SCHOOL,
MADISON, WIS.

AND

K. K. Chen, Ph.D., M.D.,
DIRECTOR OF PHARMACOLOGIC RESEARCH, THE LILLY RESEARCH LABORATORIES,
INDIANAPOLIS, IND.

The plant Thevetia neriifolia (Jussieu) is indigenous to South America and the West Indies, but is now cultivated in the East Indies, India, the Hawaiian Islands and West Africa, chiefly for ornamental purposes. It belongs to the family Apocynaceæ, which also gives rise to apocynum (A. cannabinum or A. androsæmifolium), oleander (Nerium oleander) and different species of strophanthus. Thevetia neriifolia is a tree 10 to 20 feet high, and bears fruits which finally yield dark brown, hard-shelled nuts, as shown in Fig. 1.

The kernels of these nuts have been known to be poisonous to men and animals since the latter half of the sixteenth century. Cases of poisoning have been described by Decourtilz,[1] Balfour and Maclagen,[1] Dumontier,[2] and Dey.[3] Various colloquial names have been assigned to the nuts according to the localities, being called be-still nuts in the Hawaiian Islands, ahouai in the Antilles, joro-joro in Dutch Guiana, lucky seed in Jamaica, cascaveleira in Brazil, bois saisi in Haiti, and pilakanir or kokilphul in India.

The first chemical study on the nuts of Thevetia neriifolia was undertaken by DeVry,[2] in 1863, who isolated from them a glucosid and named it thevetin. In spite of subsequent investigations, as carried out by Blas,[4] Weitz and Boulay,[5] Ayyar,[6] Chopra and Mukerjee,[7] and Ghatak,[8] the chemistry of thevetin is still in a realm of uncertainty and needs further exploration.

Husemann,[1] in 1876, showed that thevetin has a digitalis-like action on the heart, but he believed that it caused abscess formation upon injection. Chopra and Mukerjee[7] recently made an extensive pharmacologic study on thevetin and concluded that "the margin between the therapeutic and toxic limits seemed to be too low to warrant its safe administration." They did not determine the

* Read before the Section on Pharmacology and Therapeutics at the Eighty-fifth Annual Session of the American Medical Association, Cleveland, Ohio, June 13, 1934.

exact potency of the principle by any of the well-known assay methods.

Our interest in thevetin was initiated by one of us (H. L. A.)[9] when a child, aged 5 years, died 20 hours after eating the nuts, at the Children's Hospital, in January, 1931. The manifestations were like digitalis poisoning. It also happened that several chickens

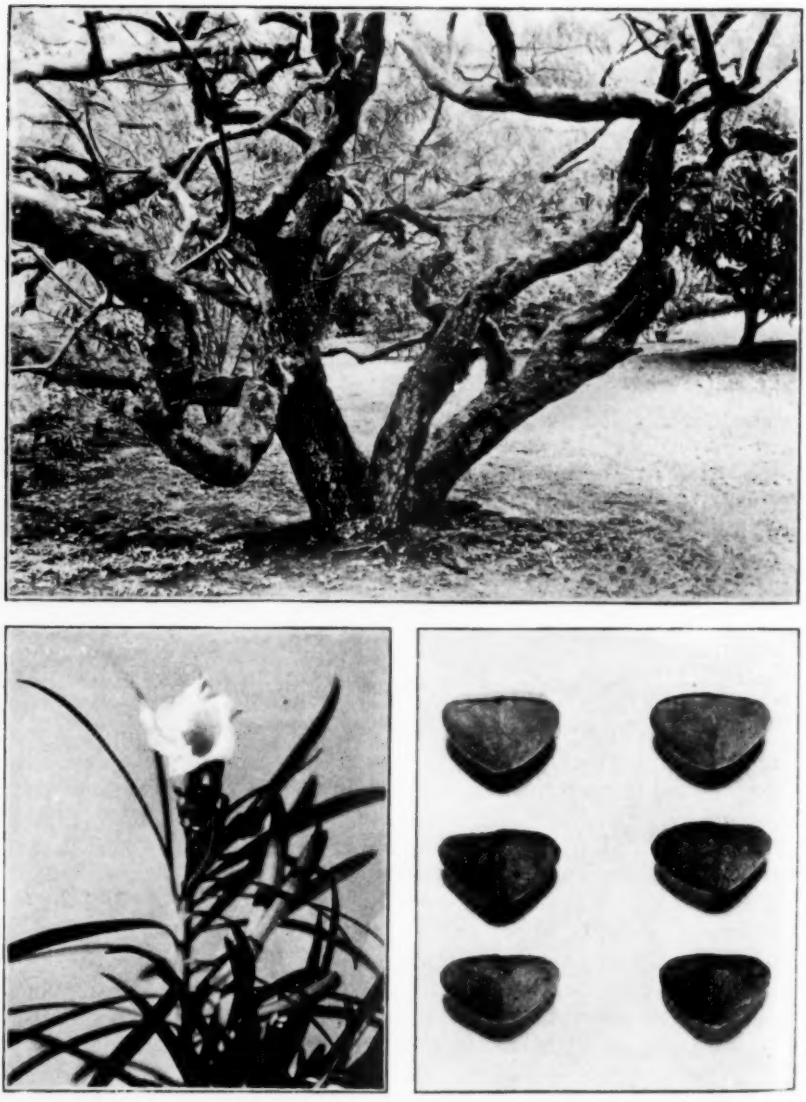

FIG. 1.—Upper, tree of Thevetia neriifolia: lower left, flower; lower right, mature nuts.

succumbed from the same cause at this child's home. A sample of the nuts was soon collected and forwarded (for chemical investigation) to the laboratory with which another one of us (K. K. C.) is associated. Chen and Chen[10] ultimately isolated thevetin and subsidiary glucosids in pure form, and subjected them to a quantitative pharmacologic evaluation.[11]

Laboratory Data. Thevetin is soluble in alcohol and less in water. It melts at about 193° C. (corrected) and has a specific rotation of $[\alpha]_D^{28}$ −62.5°. Its empirical formula is $C_{29}H_{46}O_{13}.2H_2O$. The substance is relatively stable, since a dilute aqueous solution retains its physiologic activity for more than a year.

Action on the Heart. The chief action of thevetin is on the heart. In frogs it causes systolic ventricular standstill either by injection into the lymph sac or by perfusion into the inferior vena cava. On the mammalian heart, Chopra and Mukerjee[7] observed that thevetin has a stimulant action in small amounts, but depresses and stops the ventricles in large doses. During stimulation the cardiac output and coronary outflow are both increased; but the latter diminishes when intoxication by larger doses of thevetin begins. Electrocardiograms, recorded from etherized cats while a dilute solution of thevetin was slowly injected, showed typical changes of digitalis-like action[11] such as bradycardia, inversion of *T* wave, *P–R* prolongation, *A–V* dissociation, ventricular tachycardia and, finally, ventricular fibrillation. In terms of the fatal dose, it appears to take a relatively smaller quantity of thevetin to produce the first appearance of *P–R* prolongation and maximal slowing of the heart rate than for ouabain or digitoxin.

Thevetin has a persistence of action comparable to that of ouabain as determined in cats. Of the fatal dose, 47% may remain in circulation for more than 5 hours, and 71% for more than 22 hours, but 82% may be completely eliminated in 24 hours. Hatcher[12] reported that in cats, digitalis and digitoxin might be present in the body for a full month, while the largest sublethal doses of strophanthin disappeared in a day.

In animals, thevetin is easily absorbed when it is given per os or by subcutaneous injection.

Potency. When assayed by the method of Hatcher and Brody,[13] the cat unit of thevetin is determined to be 0.85 mg. per kg.[11] With the U. S. P. frog method,[14] the glucosid has a minimal systolic dose of 0.004 to 0.005 mg. per gm. Ouabain assayed under the same laboratory conditions is shown to have a cat unit of 0.12 mg. per kg. and a minimal systolic dose of 0.005 to 0.006 mg. per gm. in frogs. Based upon the cat unit, thevetin is $\frac{1}{7}$ as toxic, but also $\frac{1}{7}$ as powerful, as ouabain.

Action on Other Organs. Aqueous solutions of thevetin are bitter to the taste. Like other cardiac glucosids, thevetin, in large doses,

causes a sustained rise in blood pressure with occurrence of vagal pulse, arrhythmia and tachycardia, as shown in Fig. 2. It induces nausea and vomiting in pigeons, cats or dogs. Thevetin in appropriate concentrations stimulates intact or isolated intestines, uteri and urinary bladder,[7,11] the action probably being on the smooth muscles.

With aseptic precautions, no necrosis occurs when thevetin is injected, either in rabbits or in men, intradermally, subcutaneously or intramuscularly.[11] Like other digitalis glucosids, it may produce a slight pain at the point of injection, but it does not cause abscess formation, as claimed by Husemann.[1]

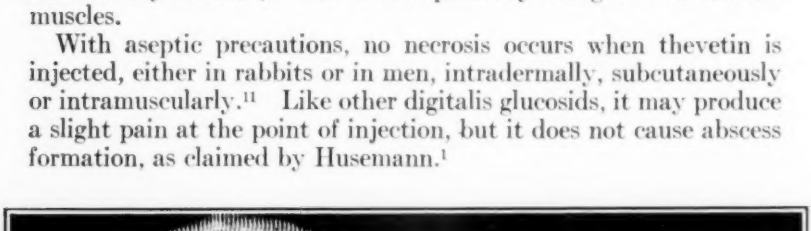

FIG. 2.—Action of thevetin on blood pressure. Cat, male, weighing 2.66 kg., was decerebrated and pithed. Both vagi were sectioned. Artificial respiration was administered. The injection of thevetin was made by the intravenous route.

Action of a Single Dose of Thevetin in Men With No Apparent Cardiac Disorders. In view of the fact that thevetin is sufficiently soluble in water, relatively stable in solutions, easily absorbed, and prompt in action, it appeared justifiable to study its action in men. Although it is less persistent than digitalis, it has at the same time less risk of cumulative action.

Upon the oral administration of thevetin to normal individuals in doses of from 1 to 5 cat units, there regularly occurred a fall in the pulse rate (Table 1, Cases 1 to 5). The degree of this fall, which ranged from 9 to 20 beats per minute, bore no direct relation to the dosage. The greatest decrease in pulse rate occurred with 2 cat units, whereas the least was with 4 cat units. A maximal effect in this direction was recorded in 2 to 3 hours; but again the time factor was not directly related to the dosage. Interestingly, heart burn was occasioned in both instances where the dose of thevetin exceeded 3 cat units in the normal subjects.

One individual (Table 1, Case 6) received 3 cat units of thevetin intramuscularly with a resultant decrease in the pulse rate of 12 per minute after 3 hours. He experienced no general subjective manifestations, but there was a dull ache at the site of injection for about 5 hours. The discomfort gave way to slight tenderness at

TABLE 1.—EFFECTS OF A SINGLE DOSE OF THEVETIN AND TINCTURE OR POWDER OF BE-SHIL NUTS.

TABLE 1.—EFFECTS OF A SINGLE DOSE OF THEVETIN AND TINCTURE OR POWDER OF BE-STILL NUTS.

Case.	Age	Sex.	Weight, pounds	Diagnosis.	Funct. capacity	Before		Preparation.	Dosage, cat units	Route.	Interval, min.	Objective results.			Subjective results.	Adverse reactions.
						P.	B.P.					P	B.P.	EKG		
1	36	M	..	No cardiovascular diagnosis	I	92	....	Powder	?	Oral	150	−30	..	..	....	0
2	35	M	..	No cardiovascular diagnosis	I	84	....	Powder	1	Oral	1 0	−17	..	..	....	0
3	23	M	..	No cardiovascular diagnosis	I	84	....	Powder	3	Oral	180	−12	..	..	....	0
4	26	M	..	No cardiovascular diagnosis	I	64	....	Powder	4	Oral	150	− 9	..	..	....	Heart burn.
5	34	M	..	No cardiovascular diagnosis	I	76	....	Powder	5	Oral	150	−13	..	..	....	Heart burn.
6	34	M	130	No cardiovascular diagnosis	I	76	....	Thevetin	1	I.M.	180	−12	..	..	....	Dull ache at site of injection.
7	26	M	156	No cardiovascular diagnosis	I	76	....	Thevetin	1	I.M.	92	−20	..	..	....	Burning, throbbing neuritic pain.
8	41	M	150	Rheumatic heart disease	III	84	130/?	Thevetin	2.5	I.V.	10	− 6	+ 2/?	+	Breathes easier	0
9	60	M	96	Arteriosclerotic heart disease	III	102	156/130	Thevetin	5	I.V.	13	−10	+10 S − 4 D	+	0	0
10*a*	18	M	165	Rheumatic heart disease (in fibrillation)	III	90	110/?	Thevetin	5	I.V.	13	−32	− 2/?	+	Less pounding	0
10*b*	..	..	..	Rhythm normal		100	110/86	Thevetin	5	I.V.	30	−40	..	..	0	0
11	62	M	190	Arteriosclerotic heart disease (parox. tachycardia)	III	146	110/84	Thevetin	5	I.V.	45	0	−12 S − 9 D	0	0	0
12	47	M	165	Luetic aortitis with regurgitation	III	84	....	Thevetin	5	I.V.	20	−20	..	+	0	More extrasystoles
13	29	M	130	Chronic nephritis with hypertension; myocard. degeneration	III	118	172/132	Thevetin	5	I.V.	..	0	0	+	0	Nodal rhythm with many ▲ extrasystoles.
14	62	M	190	Arteriosclerotic heart disease	III	84	122/?	Thevetin	5	I.V.	10 hr.	−12	−14/?	+	0	0
15	47	M	210	Arteriosclerotic heart disease	III	90	154/?	Thevetin	5	I.V.	100	−10	−12/?	+	0	0
16	41	M	143	Rheumatic heart disease	IIa	72	130/88	Thevetin	5	I.V.	20	− 8	− 6 D	+	0	0
17	53	M	132	Rheumatic heart disease	IIb	98	96/70	Thevetin	5	I.V.	40	− 2	+16 S +10 D	+	0	0
18	43	M	130	Rheumatic heart disease	IIb	68	112/?	Thevetin	5	I.V.	19	−12	+10/?	+	0	0
19	66	M	180	Arteriosclerotic heart disease	III	108	....	Thevetin	5	I.V.	90	−12	0	+	0	0
20	76	M	140	Arteriosclerotic heart disease	III	84	200/120	Thevetin	5	I.V.	4 hr.	− 8	0	+	Diuresis	0
21	70	M	139	Arteriosclerotic heart disease	III	84	198/120	Thevetin	5	I.V.	90	+ 4	..	+	0	0
22	57	M	146	Arteriosclerotic heart disease	III	76	110/?	Tincture	2	Oral	..	0	0	0	0	0
23	37	M	140	Rheumatic heart disease	IIb	76	85/?	Tincture	1 3	Oral	Indef.	−16	0	0	0	0
24	64	M	154	Arteriosclerotic heart disease	III	76	....	Tincture	0 5	Oral	....	0	0	0	0	0
25	64	M	187	Arteriosclerotic heart disease	III	56	155/?	Tincture	0 6	Oral	..	0	0	0	0	0
26	73	M	200	Arteriosclerotic heart disease	III	124	174/?	Solution	1 6	Oral	Indef.	−18	0	+	?	0
27	42	M	142	Rheumatic heart disease	IIb	80	130/60	Solution	0 5	Oral	....	0	0	0	0	0
28*a*	65	M	118	Thyrotoxic heart disease	IIb	72	170/?	Solution	0 5	Oral	Indef.	− 8	0	0	Breathes easier	0
28*b*	..	..	..	.....	..	72	170/?	Tincture	0 5	Oral	..	0	0	0	0	0
29	50	M	140	Rheumatic heart disease	III	92	120/?	Solution	1 6	Oral	12 hr.	−12	0	+	0	0
30	43	M	239	Rheumatic heart disease	IIb	72	140/?	Solution	0 6	Oral	....	0	0	0	0	0

the end of 5 hours. A second individual (Table 1, Case 7) was given 5 cat units of thevetin intramuscularly. The pulse rate began to decline 17 minutes after the injection into the left deltoid and reached its maximal slowing of 20 beats per minute in 92 minutes. Burning, shooting neuritic pains with muscular twitching developed in the left arm and persisted with some abatement throughout the day. On the following day there remained only slight residual tenderness at the site of injection.

Action of a Single Dose of Thevetin and Other Preparations of Be-still Nuts in Patients With Cardiac Disease. With the safe background of pharmacologic support, it was deemed wise not to exhaust the study of the normal subject in his responses to the derivatives of be-still nuts but to proceed immediately to the logical clinical application of these substances in the treatment of cardiac affections.

Since poisoning has occurred by eating be-still nuts, it becomes apparent that thevetin is easily absorbed from the gastro-intestinal tract. This is well borne out by the results of animal experiments. Studies were, therefore, carried out by either intravenous injection or oral administration of pure thevetin. For the latter purpose, a solution of thevetin in 65% alcohol by volume was prepared. In addition, a tincture of the defatted kernels and the powder of the same (dispensed in capsules) were employed by mouth. Each preparation was so standardized (physiologically) that each cubic centimeter or capsule was equal to 1 cat unit.

To test the influence of a single dose of these products, 25 observations were made upon 23 patients with a variety of cardiovascular diseases. The results are grouped in Table 1. It will be observed that with a single exception (Case 8), the intravenous injections of thevetin were in doses of 5 cat units, whereas the alcoholic solution of thevetin and tincture of Thevetia were given orally in doses of 0.5 to 2 cat units. Accordingly deductions must be drawn separately and with due consideration for the discrepancy.

A fall in pulse rate succeeded the intravenous administration of a single dose of thevetin in 12 of 15 instances (14 patients). No decrease occurred in 2 and a rise was observed in 1 patient. The maximal fall appeared in less than 45 minutes in 9 observations. This point was deferred to 10 hours in 1 instance. The degree of pulse fall ranged from 2 to 40 beats per minute. As evidence that the cardiac rhythm played no decisive rôle in this direction among these patients may be cited Case 10. When the normal rhythm was restored in this patient, a greater response to 5 cat units of thevetin was observed than during a period of auricular fibrillation (40 as compared with 32). The blood pressure changes were equivocal; but the circumstance of equal numbers (4) with a fall in systolic blood pressure as with a rise should be remarked. Three patients showed no effect and 1 (Case 16) had a fall in diastolic pressure only. Of 14 patients, 13 showed some electrocardio-

graphic changes. The details of this phase of the study will be elaborated in the consideration of the treatment of cardiac decompensation, but in this connection it should be noted that only 2 patients (Cases 12 and 13) showed adverse results to a single dose of thevetin administered intravenously, and both of these had extrasystoles. Case 13 will demand further discussion, because of serious faults in conduction that attended the continued use of thevetin. Subjective improvement after a single dose of thevetin was volunteered by 3 patients and included relief of dyspnea, quieter cardiac activity and diuresis.

Tincture of Thevetia and the alcoholic solution of thevetin were administered to 9 patients (10 observations). The dosage was so small (0.5 to 2 cat units) that it is not surprising to note only 4 instances of lower pulse rate and 2 of altered electrocardiograms in response to isolated doses by mouth. One patient volunteered the statement of relief of dyspnea. Actually the interest in this limited group of patients rests in other directions which receive later consideration.

Action of Thevetin and Other Preparations of Be-still Nuts in Cardiac Decompensation. In Table 2 the results of the treatment of cardiac decompensation have been analyzed. Twenty-three patients comprised the group, which includes such patients from Table 1 (Case 8 on) as suffered from cardiac decompensation. In general, they represent the usual run of patients admitted to a general hospital for this condition. Their etiologic background covers the commoner causes of chronic myocardial degeneration, and the selection of subjects was based only upon the exclusion of definitely digitalized patients. Two of the group had been on maintenance levels of digitalis. Twenty-five periods of observation were available upon the 23 patients. In all patients tolerance was estimated upon body weight, and in the average instance theoretic tolerance was sought in 5 days. Regardless of the preparation or the route of administration, the cat unit equivalent served as the standard of dosage. The individual dose of thevetin never exceeded 5 cat units nor the daily total 10 cat units.

Insofar as the pulse response was concerned, 13 to 14 patients receiving thevetin intravenously showed slowing of the rate of from 2 to 52 beats per minute. These figures represent the radial pulse rates. The apical rates were likewise slowed and, as a rule, the pulse deficit in auricular fibrillation materially reduced. A single patient suffering from auricular paroxysmal tachycardia (Case 11) showed no fall in the pulse rate. With the oral preparations, tincture of Thevetia and the alcoholic solution of thevetin, a slowing of the pulse, ranging from 4 to 48 beats per minute, was observed in 8 of 9 patients. With 3 exceptions (Cases 22, 26 and 29), the doses of these oral preparations were relatively small or they were utilized for the maintenance of circulatory balance (Fig. 3).

TABLE 2.—ANALYSIS OF THE EFFECTS OF THEVETIN OR TINCTURE OF BE-STILL NUTS ADMINISTERED IN CARDIAC DECOMPENSATION.

Case.	Diagnosis.	Time decomp.	Recent digitalis.	Rhythm.	Funct. capacity.	Before. Wt., pounds	P.	B.P.	V.P.	EKG. P-R.	EKG. T	EKG. S-T.	Preparation.	Dosage, rat units.	Rt.	Interval.	Objective results. P.	B.P.	V.P.	EKG. P-R.	EKG. T.	EKG. S-T.	EKG. Q-R-S.	Rhythm.	Miscell.	Subjective results.	Adverse reactions.
8	Rheu. heart dis.	4 mos.	Maintenance	Aur. fibr.	III	150	84	130/?	16	..	↓ 1, 2	↓ 1, 2	Thevetin	2.5	I.V.	10 min.	−6	+2/?	0	...	0	0	+	0	0	Less dysp.	0
9	Art.scler. heart dis.	3 wks.	None	Occas. extrasys.	III	96	102	156/130	12	0.16	All ↓	1 ↓	Thevetin	5	I.V.	13 min.	−10	+10 S −4 D	−3	+	0	0	0	No extrasys.	0	0	0
10*a*	Rheu. heart dis.	5 mos.	Irreg.	Aur. fibr.	III	165	90	110/?	..	..	1	1	Thevetin	5	I.V.	13	−32	−2/?	..	..	1	1	0	0	0	Less pounding	0
10*b*				Regular	III	165	100	110/86	..	..	=	↓	Thevetin	5	I.V.	39 min.	−40	..	..	..	↓	↓					0
11	Art.scler. heart dis.	7 mos.	None	Aur. fibr., then aur. tachycar.	III	190	146	110/84	..	0.17	1 ↓	n/1	Thevetin	10	I.V.	3¼ hrs.	0	−12 S −9 D	..	0	0	0	0	Few dropped beats	0	0	0
12	Luetic heart dis.	15 mos.	None	Complete block; extrasys.	III	165	84	..	12	..	2, 3 ↓	2, 3 ↓	Thevetin	5	I.V.	20 min.	−20	..	..	..	0	0	0	More extrasys.	0	0	Incr. extrasys.
13	Chronic nephritis with hypertension; myoc. degeneration	6 wks.	Indef.	Occas. extrasys.; bun.-br. block	III	130	118	172/132	18	..	..	..	Thevetin	15	I.V.	47 hrs.	−52	−18 S −72 D	−2	..	↑↓	All ↓	+	Nodal altern. extrasys.	Most bizarre	0	Remark. arrhythmia; disappeared in 6 days.
14	Art.scler. heart dis.	9 mos.	None	Aur. fibr.	III	190	84	122/?	..	..	..	..	Thevetin	15	I.V.	2 days	−18	−14 S ? D	..	..	..	..	..	...	..	...	0
15	Art.scler. heart dis.	12 yrs.	Irreg.	Many extrasys.; bun.-br. block	III	210	90	154/?	16	0.14	All ↑↓	1, 2 ↓ 3 ↑	Thevetin	37.5	I.V.	12 days	−8	+10 S ? D	−2	+	1 ↓	1 ↓ 3 ↑	+	0	0	Temporary gain, then slump but less dysp.	Cramps and diarrhea for 1 day; not continued.
16	Rheu. heart dis.	2 yrs.	None	Regular	II*a*	143	72	130/88	10	0.20	3 ↓	3 cove	Thevetin	20	I.V.	3 days	−4	..	−2	+	2 ↑↓	3 cove	+	0	0	Less dysp.	0
17	Rheu. heart dis.	14 mos.	None	Regular	II*b*	132	98	96/70	12	0.13	3 ↓	1, 2 ↑↓	Thevetin	5	I.V.	40 min.	−2	+16 S −10 D	−1	+	0	0	0	Occas. extrasys.	0	0	0
18	Rheu. heart dis.	2 mos.	Indef.	Aur. fibr.; many extrasys.	II*b*	130	68	112/?	13	..	All ↑↓	All ↓	Thevetin	15	I.V.	25 hrs.	−22	..	0	...	All ↓	0	0	More extrasys.	0	Early impr.	More extrasys.; died after 3d injection.

19	Art.scler. heart dis.	2 yrs.	5.5 cc. of tincture	Aur. fibr.	III	180	108	..	14	..	1, 2 =	..	Thevetin	30	I.V.	5 days	−44	..	0	..	All ↓	cove	0	0	Diuresis	Marked impr. in dysp.	0
20	Art.scler. heart dis.	9 mos.	Little infusion	Regular	III	140	96	110/104	..	0	17	1, 2 ↑↓	1, 2 ↓	Thevetin	30	I.V.	6 days	−36	− 6 S −14 D	..	+	0	1 ↑	..	Occas. extrasys.	Diuresis	Edema and dyspnea decreased	Anorexia; diarrhea without cramps 1 day; disappeared.
21	Art.scler. heart dis.	4½ mos.	None	Regular; bun.-br. block	III	139	84	198/120	16	0	18	1 ↓	1 ↑ 3 ↓	Thevetin	20	I.V.	4 days	−30	− 3 S −20 D	− 2	+	0	−	+	0	Diuresis	Able to lie down and edema much less	Anorexia and abd. discomfort with diarrhea on 5th day.
22	Art.scler. heart dis.	2½ yrs.	None	Many extrasys.	III	146	76	110/?	16	0	14	1 ↓	2 ↓	Tincture	22	O.	4 days	−20	−10 S ? D	− 6	+	0	0	+	More extrasys.	Slight diuresis	Resp.easier	Diarrhea 2d day; nausea, emesis 4th day; more extrasys.
23	Rheu. heart dis.	2 yrs.	Small doses for 2 yrs.	Regular	IIb	140	76	85/?	7	..		..	..	Tincture	5 3	O.	1 day	−16	+5/?	− 1	..	..	..	..	0	0	0	Cramps persisted 2 days after discontinuing.
24	Art.scler. heart dis.	5 yrs.	Irreg. but long dur.	Aur. fibr.; bun.-br. block; extrasys.	III	154	76	185/?	14	..		1 ↓	1 ↓ 3 ↑	Tincture	1.5 daily	O.	37 days	−14	−40/?	0	..	0	1, 3 =	+	0	0	Circ. equili. held	Cramps and diarrhea 37th day.
25	Art.scler. heart dis.	2 mos.	Irreg.	Aur. fibr.	III	187	56	155/?	16	..		2 ↑↓ 3 ↓	1, 2 ↓	Tincture	6	O.	3 days	+ 8	+11	0	..	..	..	..	0	0	0	Nausea, vomit., but had occur'd before.
26	Art.scler. heart dis.	1 yr.	None	Aur. fibr.; many extrasys.	III	200	124	174/?	20	..		..	..	Solution	40	O.	5 days	−48	+2/?	− 8	..	..	1 ↓	+	0	Diuresis	Dysp. controlled; edema less	Slight anorexia on 6th day; quest. nausea.
27	Rheu. heart dis.	1 yr.	Irregular 1 yr.	Regular	IIb	142	80	130/60	14	0	18	1 ↑↓ 3 ↓	1, 2 ↓	Solution	1.5 daily	O.	16 days	−16	− 8 S −12 D	− 4	−	All ↓	cove 3 ↓	+	0	0	Cir. equili. held	0
28a	Thyrotox. heart dis.	3 yrs.	Infusion periodic.	Aur. fibr.	IIb	118	72	170/?	..	..		..	..	Solution	1.5 daily	O.	3 days	−10	..	..	..	..	..	..	0	0	Circ. equili. held. Dys. better	0
28b						...	84	150/?	..	..		..	..	Tincture	1.5 daily	O.	4 days	− 8	..	..	..	..	..	..	...	..		
29	Rheu. heart dis.	6 yrs.	Maintenance	Aur. fibr.	III	140	92	124/?	16	..		1, 2 ↓	1, 2 ↓ 3 ↑	Solution	20	O.	3 days	−32	−4/?	−10	..	All ↓	0	+	0	Diuresis	Edema and dyspnea controlled	Abd. discomfort 3d day; nausea and diarrhea.
30	Rheu. heart dis.	20 mos.	Irreg.	Aur. fibr.	IIb	239	72	140/?	12	..		3 ↓	1, 2 ↓	Solution then tincture	2 daily	O.	5 16 days	− 4 −12	−15/?	− 6	..	All ↓	0	+	0	0	Circ. equili. held	0

CODE: Increase, +; decrease, −; no change, 0; elevated, ↑; depressed or inverted, ↓; diphasic, ↑↓; flat, =; single dose, '; Rt., route; I.V., intravenous; O., oral.

The changes in blood pressure in the whole group were not decisive. Decreases were observed in 11 instances and increases in 7. As anticipated, a fall in venous pressure was found in 12 of 17 recorded readings.

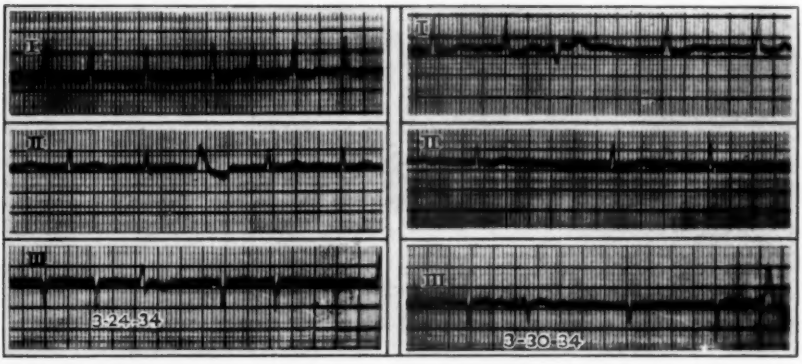

FIG. 3.—Electrocardiograms of Case 26, demonstrating the response to the oral administration of alcoholic solution of thevetin.

The electrocardiographic observations were especially illuminating. Demonstrable changes were observed in 19 instances. Lengthening of the auriculoventricular conduction time was noted 7 times; in 1 patient it was slightly shortened. If the cases of auricular

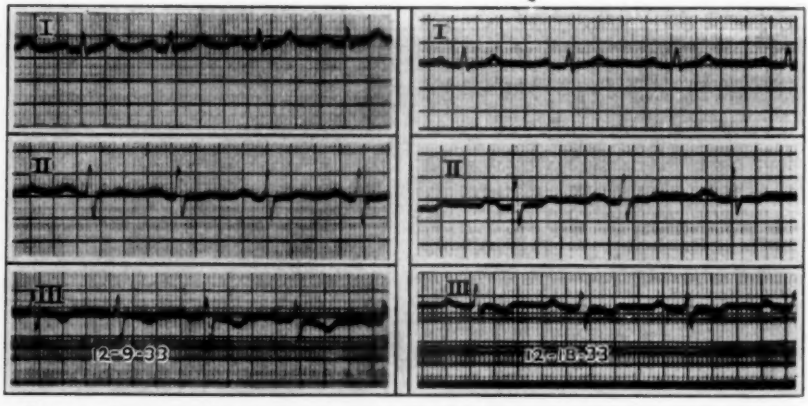

FIG. 4.—Electrocardiograms of Case 16, demonstrating prolongation of the *P–R* interval in response to the intravenous administration of thevetin.

fibrillation, 8 in number, be excluded from the group of 17 where a recheck was available, only 2 instances are left in which vagal stimulation was not manifest by an increased *P–R* interval after drugs of this series. In Case 16, the *P–R* interval was lengthened

from 0.2 to 0.25 second (Fig. 4). The electrocardiograms of 9 patients underwent changes in the *T* waves; in 5 of these, all *T* waves became negative. Deviation of the *S–T* segments occurred in 9 instances and significant coving appeared in 3 (2 included in the 9 with *S–T* deviation). Alterations in the *Q–R–S* complexes appeared in the electrocardiograms of 11 patients in this group. These changes included modifications of the time factors as well as the form of the *Q–R–S* waves. Five patients showed more frequent extrasystoles (Cases 12, 18 and 22) or extrasystoles only after these drugs (Cases 17 and 20). Case 9 showed an abolition of extrasystoles and Case 11 a few dropped beats after thevetin.

The control of decompensation was marked in 9 patients. In 6 water-logged subjects, diuresis resulted early and was a conspicuous feature in the movement toward restored circulatory balance. Dyspnea was relieved in 10 individuals. In 4 instances it was noted that these drugs were capable of maintaining circulatory equilibrium when utilized in place of digitalis at maintenance levels.

Adverse Reactions to the Various Preparations of Be-still Nuts in Cardiac Decompensation. The untoward effects recorded may be grouped under two headings, *viz.*, disturbances of conduction and gastro-intestinal disorders. The simple extrasystolic arrhythmias so common as toxic manifestations to drugs of digitalis-like action may be dismissed without further comment; but the conduction changes in Case 13 were so unusual and bizarre as to deserve special comment. A hypertensive nephritic with myocardial degeneration and pronounced congestive failure had presented only bundle-branch block and occasional extrasystoles prior to the institution of the thevetin therapy. Fifteen cat units had been administered intravenously over a period of 47 hours, when coincident with a slowing of the pulse from 130 to 78 beats per minute, there appeared to auscultation a peculiar alteration of cardiac action. The electrocardiogram (Fig. 5) was revealing. There had apparently occurred a change in the pacemaker with an institution of nodal rhythm, and each regular *Q–R–S* complex was succeeded by an extrasystole. The bundle-branch block persisted and there was some debate as to the possible existence of an alternating bundle-branch block. The patient showed no subjective nor objective handicap and sinus rhythm was resumed 6 days after the discontinuance of thevetin.

In Case 18, death succeeded the third intravenous injection of 5 cat units of thevetin. The patient suffering from rheumatic heart disease with auricular fibrillation, showed a sharp fall in the radial pulse rate subsequent to the second intravenous dose of thevetin on the first day. Following the prescribed plan of electrocardiographic control of this intravenous medication, a third dose was administered on the second day (the ventricular rate having

risen from 72 to 75 to 80). Within a few moments the patient died. Necropsy permission was denied and the true explanation of this death must remain unrevealed. The only suggestion of an altered myocardial irritability lay in the more frequent extrasystoles which appeared in the electrocardiogram taken less than one-half hour before death. In no other detail was there a change from the preceding tracings except for the described slightly increased ventricular discharge.

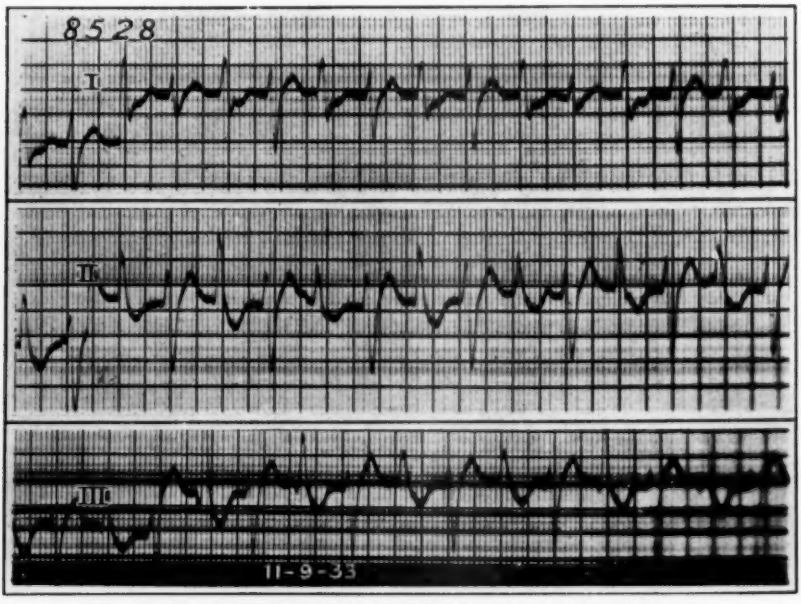

FIG. 5.—Electrocardiogram of Case 13 after 15 cat units of thevetin.

The patients receiving thevetin intravenously were remarkably free from gastro-intestinal symptoms of intoxication; anorexia, abdominal discomfort or cramps and diarrhea, singly or collectively, occurred in only 3 patients (Cases 15, 20 and 21). In 2 of these (Cases 15 and 20), the gastro-intestinal unrest subsided in spite of the continuance of the drug. The case for tincture of Thevetia and the alcoholic solution of thevetin by mouth was not as clearly cut. The first 2 patients receiving the tincture (Cases 22 and 23) suffered from cramps or diarrhea, nausea and vomiting on the 4th or 5th day. The 3d one taking the tincture (Case 24) had cramps and diarrhea on the 37th day. The 4th (Case 25) had a continuance of nausea and vomiting. Two other patients receiving maintenance dosage of the galenical preparation (Cases 28 and 30) were able to continue without discomfort. Likewise these same 2 patients had taken the alcoholic solution of thevetin for 3 and

5 days, respectively, with no inconvenience. Another patient (Case 26) was carried to theoretic tolerance and satisfactory therapeutic effect on the alcoholic solution of thevetin, with a slight sense of nausea on the last day. A 4th (Case 27) experienced no discomfort on effective maintenance levels of this form of thevetin; but a 5th (Case 29) had abdominal discomfort on the 3d day and nausea and vomiting thereafter.

Apparently, then, tincture of Thevetia possesses additional ingredients which are irritable to the gastro-intestinal tract. This seems enough to preclude its clinical use. The objections to the alcoholic solution of thevetin are less clearly defined and a much larger series of observations is required to answer this question. It is entirely possible that both may be found wanting just as were squill, apocynum and convallaria by White and his associates.[15,16]

Summary and Conclusions. Thevetin, a cardiac glucosid, has been isolated from the be-still nuts and its physical, chemical and pharmacologic properties established. Of particular promise is its digitalis-like action. By biologic assay its potency has been fixed as $\frac{1}{7}$ that of ouabain. It is likewise $\frac{1}{7}$ as toxic. Its action is more prompt and less sustained than digitalis. These facts serve as guides to its possible clinical applications and limitations.

The clinical trial of thevetin and other preparations of the be-still nuts in a group of 23 patients suffering from cardiac decompensation has justified certain deductions:

1. Thevetin and other preparations of the be-still nuts slow the heart rate in the presence of the normal conduction mechanism or of auricular fibrillation. In a single case of auricular paroxysmal tachycardia, no reduction of the cardiac rate attended the use of thevetin.

2. Electrocardiographic studies of patients receiving these preparations closely parallel the results of digitalis therapy. Lengthening of the *P–R* interval, inversion of the *T* wave, deviations of the *S–T* segments and alterations in the *Q–R–S* complexes are characteristic.

3. Compensation is restored and maintained in appropriate cases of congestive heart failure. Diuresis occurs in the course of this altered circulatory balance.

4. In the clinical use of thevetin more or less serious conduction faults may develop occasionally, even though every reasonable precaution has been exercised. This hazard may be minimized, if the potency and the comparative strength of this glucosid be borne in mind when it is used alone or in combination with drugs of similar action.

5. The irritant qualities of thevetin apparently deny its availability for intramuscular use.

6. The intravenous administration of thevetin has not been attended by evidence of local irritation or thrombosis.

7. Thevetin affords an added reliable and potent cardiac glucosid for intravenous use.

8. Extended study is necessary to determine the value of pure thevetin for oral use. The galenical preparations of defatted kernels, such as the tincture and the powder, appear to be clinically unsuitable because they frequently cause gastro-intestinal disturbances such as cramps and diarrhea.

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QUINIDIN AND STRYCHNIN IN THE TREATMENT OF PREMATURE CONTRACTIONS.*

By J. Bailey Carter, M.D.,
CLINICAL INSTRUCTOR IN MEDICINE, RUSH MEDICAL COLLEGE; ASSOCIATE IN MEDICINE, COOK COUNTY HOSPITAL,

AND

Eugene F. Traut, M.D.,
ASSISTANT CLINICAL PROFESSOR IN MEDICINE, RUSH MEDICAL COLLEGE; ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL,
CHICAGO, ILL.

(From the Department of Cardiology, Rush Medical College.)

One of the most unsatisfactory complaints with which the physician must deal from the standpoint of therapeutics is extrasystolic arrhythmia. While most of these cases are not of serious moment, in some the extrasystoles may recur so frequently that the resulting pulse deficit causes symptoms that demand treatment. A pro-

* Preliminary report was given before the Chicago Society of Internal Medicine, March 27, 1933.

longed search has therefore been made for means of affording relief to these sufferers.

Quinin has been used for many years by physicians on account of its supposed sedative action on the heart. Oppolzer,[1] the Viennese clinician, states, "The best and most powerful factors in dealing with heart patients are three: rest, digitalis, and quinine." Ludwig Traube[2] added quinin to digitalis to prevent or to relieve the disagreeable action of digitalis on the stomach. Many other clinicians observed that by using digitalis with quinin they could give larger doses without getting disagreeable symptoms.

Although clinicians, for the most part,* seem to have forgotten about quinin, due to the lack of proper indications for its use, and also because it was shown experimentally by Santesson[3] and by Stokvis,[4] to have a paralyzing effect on the heart muscle, it was recalled to Wenckebach's attention in 1912 by a Dutch merchant, who used it to control his paroxysmal attacks of auricular fibrillation. Wenckebach,[6] in 1914, was apparently the first to record its deliberate use in the treatment of auricular fibrillation. He exploited the use of the very quality which had caused the older clinicians to abandon the drug. The effects of quinin in fibrillation were disappointing; however, the depressing, paralyzing action of the drug had a very favorable effect on the hyperactivity of the heart. He decided to try this form of treatment in other arrhythmias due to hyperkinesis.

It is well known that until this time there was no generally satisfactory drug or method of treating the most common of arrhythmias. Wenckebach,[7] in searching for specific drugs against extrasystoles, found that strychnin was often of value. However, strychnin, independently and alone, at times, was found to be absolutely ineffective. He then tried a combination of quinin and strychnin, writing in 1923,[8] "My experience with this treatment since the year 1915 has been so favorable that I am convinced that whoever will try it will come to the same conclusion."

Stimulated by these observations, Frey,[10] in 1918, studied the clinical pharmacology of the various cinchona derivatives in patients with auricular fibrillation. He found quinidin to be much more powerful than quinin; the difference appearing to be merely quantitative. Finding quinidin to be the most effective therapeutic agent, he recommended that the drug in the form of its more soluble sulphate be used clinically.

The drug's pharmacologic actions on the heart, so far as they are at present understood,[11, 12] are as follows:[13] (1) Mild inhibition of the vagus; (2) lowered rate of sinus impulse discharge; (3) slight decrease in A–V conduction; (4) lengthening of the refractory period of cardiac muscle and slowed conduction therein; (5) lessened ex-

* H. Hochhaus[5] in 1907 recommended quinin combined with digitalis or camphor in the treatment of extrasystoles.

citability of the cardiac muscle;[14, 15, 16] (6) dilatation of the coronary arteries.*[21]

Digitalis in toxic doses brings the heart to a standstill in systole; quinidin in diastole. In smaller doses, it leads to a definite depression of the strength of the heart beat. The principal effect of quinidin lasts for only 1 or 2 days. Wiechmann[17] states that excretion, principally in the urine, begins promptly and is greatest during the first 24 hours.

Strychnin, in therapeutic doses, according to Sollmann[18] is without effect upon the cardiovascular system. Kikuchi,[19] however, reports that strychnin produces a marked increase in the absolute strength of the frog's heart. This is in accord with the therapeutic results repeatedly observed by clinicians who have given the drug empirically as a cardiovascular tonic in spite of contrary opinions from experimental work on anesthetized animals.

White, Marvin and Burwell[20] incidentally mention the use of quinidin in 1 case of premature ventricular contractions which was materially aided. Boden and Neukirch[21] report success in the treatment of extrasystoles. Smith[22] (1921) states: "Drugs do not seem to influence their prevalence," and Rogers,[23] shortly afterward, writes: "I know of no drug which will directly improve this cardiac condition." The following year Smith[24] reports the use of quinidin in 20 patients with premature contractions. In 10 patients the irregularity was eliminated, while in 7 their frequency was diminished. Singer and Winterberg[25] report favorably, whereas Viko, Marvin and White,[26] in 1923, state: "The data at present available are inconclusive regarding the value of quinidine in treating cases with premature beats." Kerr and Bruck[27] report several cases of extrasystoles successfully treated with quinidin. Musser,[28] in treating a considerable series, had very good results in 60% of his cases without noting bad results from its use. Barrier[29] was able to abolish them in more than 90% of cases. Bishop[30] feels that it is of distinct clinical value, and Maynard[31] advises its use in the treatment of these patients. McGuire's[32] experience with 50 cases of extrasystoles was favorable; if success occurred it was usually noted within the first 24 hours. Lewis[33] states: "The only drug that frequently stops extrasystoles is quinidine given in doses of 2 to 5 grains twice or thrice daily." He warns that, "Digitalis should not be used."

Other observers have not obtained such good results. Wolferth[34] believes that quinidin has a very limited field of usefulness in the extrasystolic arrhythmias. Otto and Gold[35] state: "The results of our studies indicate that both of these drugs (quinin and quinidin) have a limited field of usefulness in the treatment of patients with premature contractions and, furthermore, that digitalis deserves a

* Quinin dilates bloodvessels in general and lowers the blood pressure.[25] Presumably quinidin has the same effect.

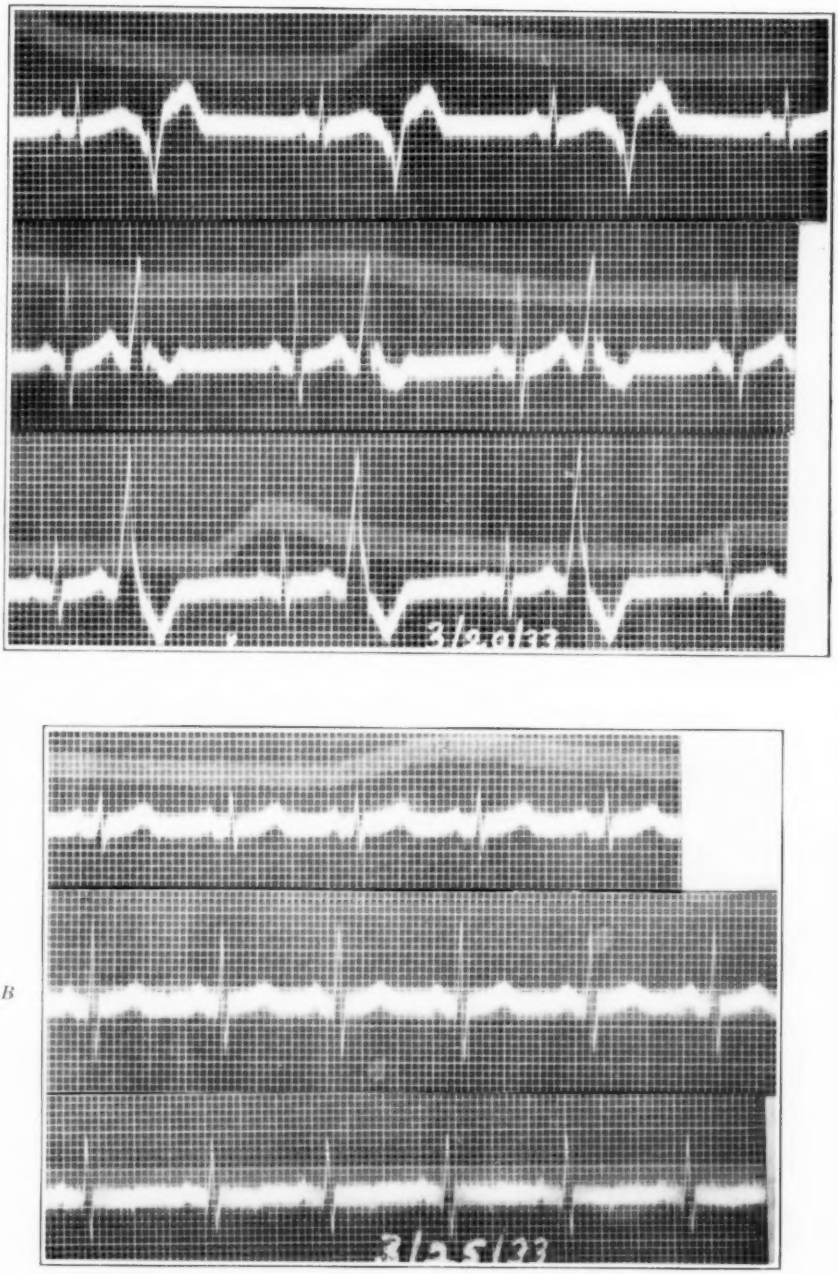

FIG. 1.—Electrocardiograms of Case 2. *A* is the record before medication; *B* is the record after medication.

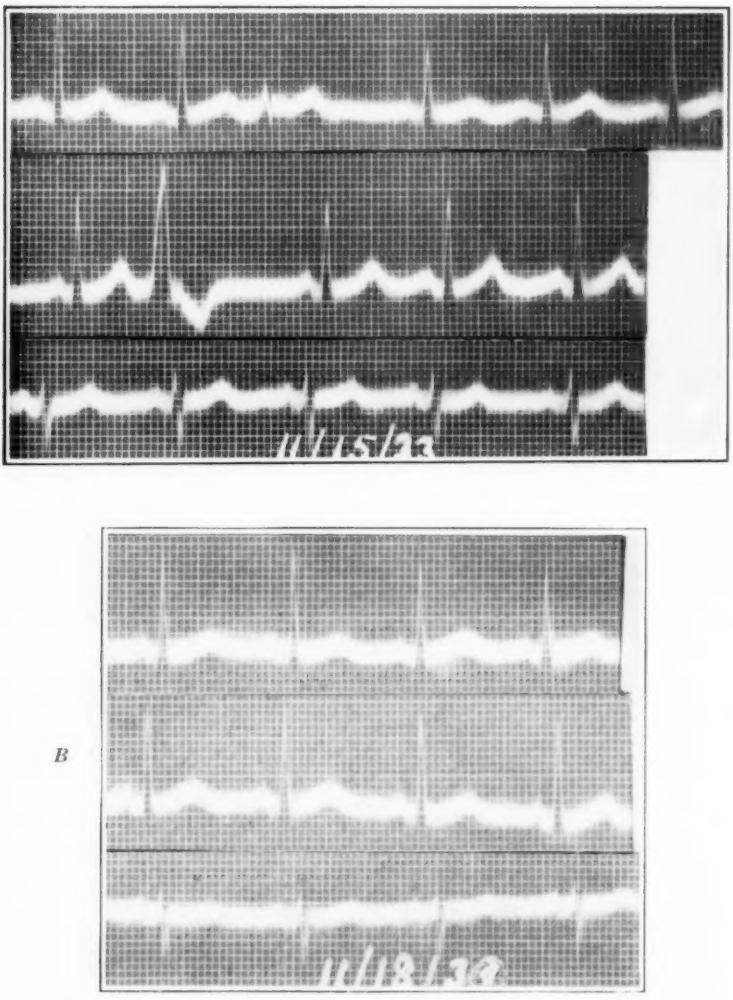

FIG. 2.—Electrocardiograms of Case 3. *A* is the record before medication; *B* is the record after medication.

more prominent place in the treatment of the premature contraction than it has heretofore received." Korns[36] reports a case of paroxysmal tachycardia in which the dose of quinidin required to control the associated extrasystoles was too high to be practicable.

No further reports on the combined use of quinidin and strychnin have been found in the literature.

Case Abstract. A laborer, aged 60, was first seen on August 15, 1931. He had had 6 attacks of syncope during the preceding 3 years. The last attack, 1 month previously, occurred after an hour's walk. It was longer and more severe than usual. These attacks lasted from 15 to 30 minutes following exertion such as walking, but had occurred while the patient was quietly resting. He usually felt the attack coming on, when everything around him would "start swimming around." As a rule he did not completely lose consciousness, although he was unable to move because of faintness. Once he fell, injuring his head. Palpitation, following exertion and also while lying quietly in bed, had been noticed during the previous 3 years. Weakness and dyspnea on climbing stairs and dull, aching pains in the calves of the legs had been present for 2 months. These were as severe in bed as when walking and had frequently kept him awake for 3 or 4 hours at night. Weakness had been more marked since his last attack of syncope. The patient felt that he was becoming progressively worse. There were no other complaints. He had had scarlet fever at 21, typhoid fever at 37, influenza at 49, and again at 56 years. There was no history of rheumatism, sore throat, diphtheria or pneumonia.

The pupils reacted to light and in accommodation. The left pupil was slightly notched. The cervical veins were engorged. The chest was fixed in inspiration. The lungs were slightly hyperresonant with transient subcrepitant râles in both bases posteriorly. There was a palpable impulse in the suprasternal notch. The point of maximum impulse of the apex beat was not visible or palpable. The lower sternum was resonant. The left heart border was 1 cm. outside the midclavicular line in the 5th interspace. The right border was at the right edge of the sternum. There were no murmurs; no thrill. The aortic second sound was ringing. The impulse at the apex was 64, at the wrist 28 per minute. The rhythm was irregular, almost every alternate beat being an extrasystole. Radial and carotid vessels were moderately thickened. Blood pressure taken at a later date was 140/90. All deep reflexes were brisk. There were no other significant clinical findings. Wassermann and urine examinations were negative. The diagnosis was arteriosclerotic heart disease, cardiac enlargement, ventricular premature contractions, type 2b.

On August 15, 1931, an electrocardiogram was taken. On August 22, 1931, the patient was given strychnin sulphate, gr. $\frac{1}{60}$, 3 times daily for 1 week. He felt improved but was still weak with many extrasystoles and a pulse deficit of 48; the apical pulse being 80, the radial pulse 32 per minute. The strychnin was continued, and in addition he was given quinidin sulphate, gr. iii, twice daily, for another week. On September 5, 1931, he was definitely improved, the rhythm was regular and there was no pulse deficit; the pulse being 40 at apex and wrist. Continuing the quinidin and strychnin for a month, the rhythm was found to be regular with a pulse of 64 at wrist and apex. Another electrocardiogram at this time revealed absence of extrasystoles, but left axis deviation and myocardial damage were still evident.

The strychnin was stopped, but the quinidin (gr. iii, 3 times daily) was continued for 2 weeks. By this time, October 17, 1931, the patient was having considerable shortness of breath, palpitation, and several extra-

systoles were noted. He was advised to take both quinidin and strychnin; felt much better within 2 or 3 days and, 1 week later, October 24, 1931, the

TABLE 1.—ANALYSIS OF DATA. CASE 1.

Date.	Complaint.	Findings.	Treatment.	Remarks.
1931:				
8/15	S; W; P; D	Left heart enlarg.; freq. XS	Ekg. ordered; no medication	Ret. 1 wk.
8/22	W; D; P	Freq. XS; pulse at apex 64, wrist 28	S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/29	Impr. but weak	Freq. XS; pulse at apex 80, wrist 32	Q. gr. iii b.i.d.; S. gr. 1/60 t.i.d.	Ret. 1 wk.
9/5	Improved	Rhythm reg.; pulse 40	"	Ret. 2 wks.
9/19	About the same	Rhythm reg.	"	Ret. 2 wks.
10/3	Still weak	Rhythm reg.; pulse 64	Stop S. cont. Q.	Ret. 2 wks.
10/17	D; P on exert.; feels cold	Several XS; pulse 72	Q. cont.; start S., gr. 1/60 t.i.d.	Ret. 1 wk.
10/24	Feels much better	Rhythm reg.; pulse 68	Q. cont.; start S., gr. 1/60 t.i.d.	Ret. 2 wks.
11/7	Feels "pretty good;" P and D occas.	No arrhythmia; pulse 60	Stopped RX. for 7 days	Ret. 2 wks.
11/14	Relapse; D and W marked	Freq. XS	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Not seen
11/21	Improved	XS present	"	Ret. 1 wk.
11/28	Feels much better	XS still present	"	Ret. 2 wks.
12/12	Feels OK	Pulse 60; reg.	"	"
12/26	Feels better	No XS; pulse 60	"	"
1932:				
1/9	No Q. and S. for 3 days; felt bad; began Q. and S.; feels OK	XS present; pulse deficit	"	"
1/23	Feels OK	Few XS; pulse 60	"	"
2/9	"	"	"	"
2/20	"	"	"	"
3/5	"	Pulse: apex 60, rad. 48	"	"
3/19	"	Pulse: apex 72, rad. 60	"	"
4/2	Slight D	Pulse 48; freq. XS	"	"
4/4	Slight D	"	K. I. m. x t.i.d.	Ret. 5 days
4/9	Slight D	"	"	Ret. 2 wks.
4/23	Precordial pain; mild D; pain in legs	"	"	Ret. 3 wks.
5/7	Feels fine	Heart reg.	"	Ret. 1 mo.
5/21	Feels fine	Heart reg.	"	Ret. 1 mo.
6/8	OK except on hot days; pains in legs severe	Occasional XS; iodid rash	"	Ret. 1 mo.
7/16	D on exert.; no P	No XS	K. I. m. v t.i.d.	Ret. 2 wks.
7/30	D on exert.; no P	No XS	Add Dig. m. v t.i.d.	Ret. 1 wk.
8/6	Not feeling so well	XS q. 8 to 10th beat	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/13	Feels much better	XS about q. 60 beats	Q. gr. ii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/20	Feels better	XS q. 15 to 30 beats	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 1 wk.
8/27	Felt bad q. alt. day	XS q. 15 to 30 beats	Q. gr. iii daily; S. gr. 1/60 t.i.d.	Ret. 2 wks.
9/10	Feels very well	XS q. 120 beats	Q. gr. ii daily; S. gr. 1/30 alt. b.i.d. and t.i.d.	Ret. 2 wks.
9/18	Tinnitus; face flushed	Not seen	Q stopped; S cont.	Not seen
9/24	Feels OK	XS q. 120 beats	Q gr. i q. alt. day; S. gr. 1/30 alt. b.i.d. and t.i.d.	Ret. 2 wks.
10/8	Had a cold; many XS	XS q. 40 beats	"	Ret. 2 wks.
10/21	Feels OK	Still has XS	"	Ret. 2 wks.
11/2	Tinnitus; face red and hot	Not seen	No Q. and S. for 2 days	Felt OK
11/4	Asks for adequate Q. and S.	No XS; pulse 80	Q. gr. ii daily; S. gr. 1/30 b.i.d.	Ret. 2 wks.
11/18	Feels fairly well	Pulse 76, reg.	"	"
12/2	Better than in months; walked 2 mi.; felt OK	Rhythm reg.	Q. gr. ii q. A.M. S. gr. 1/30 q. P.M.	"
12/16	No XS for 6 wks.; Pt. OK	Rhythm reg.	"	"
1933:				
3/15	No complaints	No XS at any time	"	Ret. q. 2 wks.
10/18	No complaints	Rare XS detected	Q. and S. stopped	Ret. q. 2 wks.
12/9	No complaints	Rare XS detected	No medication	Ret. q. mo.

S = syncope. W = weakness. P = palpitation. D = dyspnea. XS = extrasystoles.

rhythm was again regular, at a rate of 68. After being free of extrasystoles for 2 weeks he was advised, on November 7, 1931, to stop both the quinidin and strychnin for 7 days. He became tired, extrasystoles developed, and he finally became so shaky, weak, and short of breath that he "could not walk across the room without puffing." Strychnin and quinidin gave symptomatic relief within a week, although extrasystoles persisted during the following 3 weeks. The pulse then remained regular for about a month. On January 3, 1932, he again tried to stop the quinidin and strychnin for 3 days, felt worse, started both drugs again, and soon felt much better. However, extrasystoles along with a pulse deficit, persisted during the following 3 months. On April 4, 1932, the strychnin and quinidin were stopped and the patient was given a saturated solution of potassium iodid (10 min. 3 times daily). He was symptomatically improved but the extrasystoles, although decreased in frequency, persisted for a month. From May 7, 1932, to July 30, 1932, the rhythm remained

TABLE 2.—SUMMARY OF ADDITIONAL CASE HISTORIES.

No.	Sex.	Age.	Symptoms—Findings or diagnosis.	Previous treatment.	Results of Q and S.	Remarks.
2	M	10	Severe headaches; dysp.; prec. pain	Br and KI, 5 mos.; no relief	Reg. rhythm for 3 wks.	Rheum. and XS recurred for 6 wks.; no Q and S and no XS 14 mos.
3	F	38	Dizziness; B.P. 240/150; marked dysp.; smothering attacks	Br, KI, $MgSO_4$ for 3 mos.; no relief	Reg. rhythm; pt. greatly improved	No Q and S, 2 wks.; XS recurred; Q and S again controlled XS; pt. followed for 2 mos.
4	M	55	XS q. 3 to 5 beats; exam. 14 x during 9 mos.	Br, QS, D, and Qx; no relief	Reg. rhythm for 1 mo.	Heart reg. when last seen 5 mos. later.
5	M	63	Angina; freq. XS; dysp.; EKG. showed cor. occl.	D and KI, 2 wks.; XS persisted; no relief	Reg. rhythm; def. relief for 3 wks.	During and after removal of 12 teeth, Q and S—no relief—and failed to control the XS.
6	M	74	Occas. precor. pain, palp.; felt stoppage of heart	D for 3 wks.; XS persisted; no relief	Reg. rhythm; compl. relief for 1 wk.	Later, during chest cold for 1 mo., Q and S gave no relief and XS persisted.
7	F	60	Dysp. and sl. edema of feet; XS q. 3 to 4 beats	D for 15 mos.; no relief; Qx reduced XS	Reg. rhythm; marked relief	Observed since 4/1/32; Q and S first given on 11/29/33; Q and S still gives relief.
8	M	73	Epileptic attacks; bigeminy-rate 80	Unknown	Reg. rhythm for 6 mos.	Reducing Q and S caused XS to recur q. 3 to 6 beats.
9	F	60	Dysp., dizzy; fullness in chest and XS for 2 yrs.	D for 6 wks.; part. relief; XS remained	Rare XS only during 1 yr.; def. relief	More active later; overfatigue then caused XS to recur even with Q and S.
10	M	65	Early heart failure; freq. XS; arteriosel.	KI for 2 wks.; no relief	Reg. rhythm; relief 3 mos.	No Q and S, 2 wks.; XS q. 4 to 5 beats, Q and S again controlled the XS.
11	F	30	Occas. attacks XS; parox. tachy.	Qx repeated; no relief	Q and S 3 dys.; relief	No attacks, 6 mos.; rare since; controlled by routine Q and S.
12	F	39	Mitr. sten.; D intox. freq. XS	No D, 2 mos.; XS persisted	Reg. rhythm; relief	Overfatigue caused XS, even with Q and S.
13	F	65	Edema def.; dysp.; XS: q. alt. beat	D and Bed, 6 wks.; no relief	XS less freq.; def. relief	Periodically for 18 mos.; Q and S decreased XS; relief.
14	M	69	HBp; palp.; XS mistaken fib.	No. cof. or tob.; no relief	Relief 3 dys.; cont. 3 wks.	No Q and S, 3 mos.; reg. rhythm; mental strain=XS; relief by Q and S.
15	F	17	Early heart failure; mitral sten.	D and KI; no relief	XS dec. freq.; def. relief	A rheum. heart with marked myocardial damage.
16	F	54	Pit. obesity; dysp.; freq. XS	D and Qx; no relief	XS persists; no relief	Q and S to toxicity; no relief; thyroid med. also failed.
17	M	62	Early heart failure	Unknown	XS dec. freq.	Def. impr. observed, 2 wks.
18	F	46	BMR—48; freq. XS	Unknown	No effect	Thyroxin cured myxedema.
19	F	18	Palp. precor. pain; rheum. ht.; freq. XS	QD; bed rest; no imp. 1 mo.	Reg. rhythm; def. relief	Tonsils out; no XS, 3 mos.; XS recurred; relief by Q and S.
20	M	63	Dyspnea; freq. XS	D; no effect	Reg. rhythm	Def. sympt. improvement.
21	M	63	Prec. pain; dizziness; puls. bigem.	Q, 2 dys.; no relief	Reg. rhythm; def. relief	No Q and S after 2 wks.; had XS from D; XS stopped by Q and S.

Br = sodium bromid.
BMR = basal metabolic rate.
Dig. (Table 1) or D (Table 2) = Tr. digitalis.
EKG. = Electrocardiogram.
HBp = Arterial hypertension.
KI = Sat. sol. of potassium iodid.
q. = every. x = times.
Q = quinidin (Table 1) and quinin sulph. (Table 2).
Qx = Quinidin sulphate (Table 2).
QD = Quinin dihydrobromid.
Q and S = Quinidin and strychnin.
Rx = Treatment. XS = Extrasystoles.

regular. Tincture of digitalis (5 min. 3 times daily) was then added to a 5 min. dose of the iodid. The patient did not feel so well and, a week later (August 6, 1932), extrasystoles every eighth or tenth beat were found. Both the iodid and digitalis were stopped and he was again given quinidin (gr. iii daily) and strychnin (gr. $\frac{1}{60}$ 3 times daily). Although the patient felt improved and extrasystoles were less frequent with this medication, they were repeatedly noted during the following 3 months. On November 4, 1932, the patient stated that he had "gotten nowhere" during the previous 6 months. He asked to be put back on an adequate dosage of quinidin and strychnin. His request was granted. He felt well and only rarely were extrasystoles noticed on biweekly examination during the following 11 months. On October 18, 1933, the quinidin and strychnin were stopped and on repeated examinations to January 26, 1934, only a rare extrasystole was found. At this time he stated that he was short of breath and felt as "he did before." From February 2, 1934, to March 9, 1934, strychnin sulphate, gr. $\frac{1}{30}$ t.i.d., with sodium bromid, gr. xv t.i.d., failed to give relief. On March 9, 1934, he was put on routine quinidin and strychnin management. He has felt well and no extrasystoles have been noted on repeated examinations to December 15, 1934.

Twenty other patients were given quinidin and strychnin; 8 were private patients and 12 selected from a series of 53 dispensary cases of extrasystoles. The arrhythmia was marked and persistent in each case. All had mild to moderately severe symptoms and signs due entirely or partially to extrasystoles. Most of them had previously tried various drugs without obtaining relief from the arrhythmia. Quinidin sulphate (gr. iii) and strychnin sulphate (gr. $\frac{1}{30}$) thrice daily were routinely administered. Treatment was entirely successful in 16 of these cases. Two cases, 16 and 18, were complete failures. In Case 16 quinidin sulphate (gr. x) and strychnin sulphate (gr. $\frac{1}{30}$) thrice daily, for 5 days, were finally given without the extrasystoles being decreased in frequency. One patient, Case 6, obtained complete relief at first, but failed to return regularly after recovery from his chest cold. One patient, Case 15, was symptomatically relieved and had fewer extrasystoles after medication although the arrhythmia persisted.

The relatively little interest that has been shown in the treatment of premature contractions is perhaps the result of the frequently quoted opinions of Mackenzie[37] and Lewis,[38] that extrasystoles are of little practical importance. Frequently the patient is reassured, the supposed prognostic insignificance of extrasystoles explained, and months or years are often allowed to elapse without relief being obtained.

Possibly the chief factor in preventing the more widespread use of quinidin is the number of warnings that have been given regarding the dangers of the drug. That these dangers have been overemphasized has been pointed out by many clinicians.[26, 36, 39, 40, 41, 42, 43] Barrier[29] mentions that induction of ventricular tachycardia and ventricular fibrillation are among the dangers of quinidin therapy, a possibility which others have considered.[14, 44] Levy[45] advises stop-

ping quinidin after the onset of a persistently high ventricular rate. That such stimulative effects are unlikely is evidenced by the experiences of several observers.[14, 42, 46, 47] White[48] has given an excellent summary of the dangers attendant on quinidin administration. He states: "Serious accidents can happen during quinidin therapy, but they are very rare and, in carefully selected cases, very unlikely." Large doses of quinidin do unduly depress the heart muscle. There is no reason to believe that in the small therapeutic dosage used here, it would have this effect. The mild depressing effect exhibited by such doses leads to a prolonged interval of rest for the heart muscle and is certainly less harmful than the secondary effects of the extrasystoles which the quinidin is used to combat. This recalls Wenckebach,[49] who said: "Our most useful and valuable drugs are poisons when given in sufficiently large doses."

In treating auricular fibrillation it was formerly the custom to produce a normal mechanism with quinidin, stop the quinidin and count those cases that return to fibrillation as failures. That this is wrong was pointed out by Barrier.[29] A similar course has frequently been followed in the treatment of extrasystoles. The quinidin and strychnin should not be stopped, but the minimal daily amount necessary for the continuation of a normal mechanism should be determined for each individual, and this dosage maintained, at least, over a considerable period. It is often important to give frequent small doses because of the rapid excretion of both drugs. Although obviously the most interesting effects of any drug are those observed in the treatment of the more severe disturbances, as the cases of extrasystoles here presented, quinidin and strychnin have proved helpful in controlling extrasystoles in otherwise normal as well as in diseased hearts. A tendency of the extrasystoles "to escape," thereby creating a demand for increasingly larger doses of quinidin, as noted by Otto and Gold,[35] has not been observed.

The advantages of the combined use of quinidin and strychnin in the control of the extrasystolic arrhythmias, as suggested by Wenckebach, seem to have been underemphasized. We can completely confirm Wenckebach's observations regarding the favorable effects of quinidin and strychnin treatment of certain patients with premature contractions.

Summary. A laborer, aged 60, with attacks of dizziness, palpitation, and syncope for 3 years, weakness, and dyspnea on exertion for 2 months, and findings of moderate arteriosclerosis, pulmonary emphysema, engorged cervical veins, slight left heart enlargement, and frequent ventricular extrasystoles, has been observed for over 40 months. With experimental precision strychnin sulphate and quinidin sulphate, were given separately, together, and discontinued. Potassium iodid alone and in combination with digitalis was tried instead of quinidin and strychnin. Together quinidin and strychnin gave the greatest freedom from extrasystoles and from

symptoms. Under these two drugs his compensation improved. Without them, with strychnin or quinidin separately, with iodid and especially with digitalis the extrasystoles increased in frequency and his condition was correspondingly worse.

Sixteen of 20 other patients with mild cardiac decompensation due to extrasystoles when similarly treated with a combination of quinidin and strychnin showed a favorable response.

NOTE.—We wish to thank Dr. Harry A. Richter for permission to include 2 cases which have been under his care.

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CARDIOVASCULAR RESPONSE TO THE SUBCUTANEOUS INJECTION OF EPINEPHRIN AND PITUITRIN IN ESSENTIAL HYPERTENSION.

By A. H. Elliot, M.D.,

RESEARCH ASSOCIATE, DEPARTMENT OF CARDIOVASCULAR RESEARCH; ATTENDING PHYSICIAN, SANTA BARBARA COTTAGE AND GENERAL HOSPITALS,

AND

F. R. Nuzum, M.D.,

DIRECTOR, DEPARTMENT OF CARDIOVASCULAR RESEARCH; MEDICAL DIRECTOR, SANTA BARBARA COTTAGE HOSPITAL, SANTA BARBARA, CALIF.

(From the Department of Cardiovascular Research, Santa Barbara Cottage Hospital.)

The cardiovascular response to the injection of epinephrin and pituitrin in normal persons has been adequately studied, but the response to such injections in essential hypertension where, aside from the question of endocrine imbalance, altered hemodynamics prevail, is worthy of study. It would be of interest to know whether a consistent qualitative or quantitative variance from the normal response obtains in this condition. We wish to report the results of such an investigation.

Method. The response was studied in 40 hospitalized patients with essential hypertension in whom the state of the arteries, the integrity of the cardiac and renal function and the lability of the blood pressure were known. Of these 25 were females who varied in age from 41 to 80, averaging 59.2. The 15 males were distributed between the ages of 34 and 80, with an average of 60. The systolic and diastolic blood pressure and the pulse rate were determined at 5-minute intervals for 60 min. in each of 32 of the above patients following the subcutaneous injection of 1 mg. (1 cc. of a 1 to 1000 solution) of epinephrin. The response to the injection of 1 cc. of obstetrical pituitrin (Parke, Davis & Co.) was studied in all of the 40 patients. Before giving the injection, the basal levels of the blood pressure and of the pulse were determined. The patient remained prone in bed throughout the observation period. All readings were made by a single observer. The pulse was counted for a full minute at each 5-minute interval.

The blood pressure was read on a mercury sphygmomanometer, and the change of sound was regarded as the diastolic pressure level. The site of injection was not massaged.

The Epinephrin Response. The subcutaneous injection of from 0.5 to 1 mg. of epinephrin in healthy individuals is followed inconstantly by a rise in systolic blood pressure, a fall in diastolic pressure with increase in pulse pressure, and a rise in pulse rate[1]. These changes may vary in intensity from a reaction which assumes alarming proportions to no response whatever, apparently dependent upon individual differences in the rate of absorption and upon the more ill-defined factor of threshold of sensitivity of the cardiovascular apparatus. The frequency with which the typical reaction occurs varies so greatly, according to the reported studies on normal persons, that a statement of its probable incidence cannot be made. In 35 patients with apparently minor functional ailments, Bauer[2] found that 7 did not show a pulse increase over 8 beats per minute, and 15 patients did not show an elevation in systolic pressure of as much as 10 mm. of Hg. Peabody *et al.*[3] studied the response in 27 normal men and in 65 soldiers with irritable hearts. A positive reaction, defined as a rise in systolic pressure or of pulse rate over 10 or 15 points together with subjective symptoms, was not encountered in the first group. In the soldiers with irritable hearts a positive reaction occurred in 60%. On the other hand, Jensen,[4] Schulten *et al.*,[5] Blumgart[6] and others have observed the occurrence of the typical response quite uniformly in normal individuals.

The normal variation being so wide, it is not surprising that observers are in disagreement as to the interpretation of the response in hypertension. One group, led by Kylin, believe that the response is inconspicuous in this condition, whereas others claim that there is a rise in blood pressure of unusual intensity following epinephrin injection. Jensen,[4] who has conducted the most careful investigation, found that his patients with hypertension fell into two clinically indistinguishable groups, depending upon their reaction to a first and to a second subcutaneous injection of epinephrin. The first group did not respond until they were given the second injection, after which an intense and prompt increase in systolic pressure occurred. The second group of patients responded in a similar manner, but to the first injection. He could not explain the lack of response to the first injection characterizing the first group. He concluded that the response exhibited by the hypertensive patients was significantly different from the slow rise and slower decrease in pressure found in normal persons.

In Chart I the average response of our patients, as observed over a period of 60 min., is represented graphically. The average systolic pressure falls slightly for a period of 35 min., after which it rises, to remain slightly above the initial level. The average diastolic pressure falls 8 mm. in 5 min., reaching a maximum decrease of

17 mm. at 45 min. At the conclusion of the observation period it is still 12 mm. below the initial level. These changes produce a pronounced increase in pulse pressure. The average pulse rate rises steadily to an increase of 13 beats per minute at the 60-minute period.

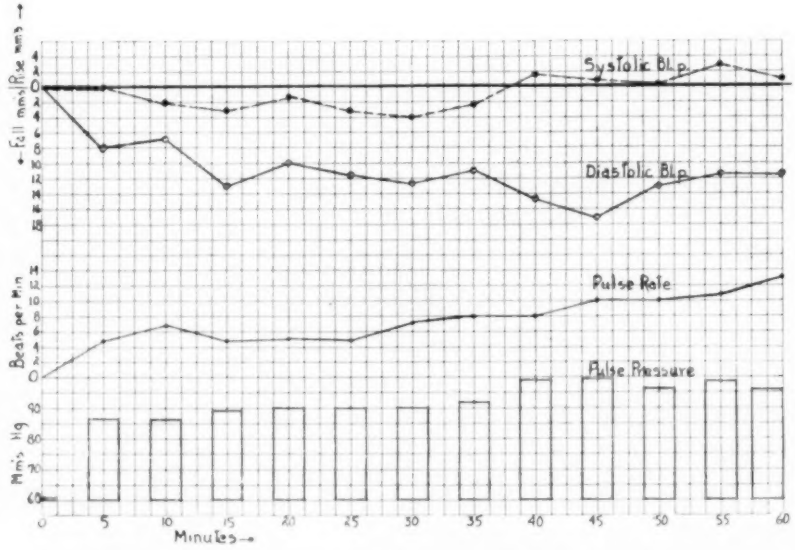

CHART I.—Average cardiovascular response to epinephrin of 32 persons with hypertension.

Analysis of the individual responses was not informative. A brisk pronounced increase (over 10 mm. of Hg in 20 min.) occurred in 5 patients only. There were no clinical characteristics to distinguish them from the remainder of the group. In general, the nature of the response was independent of previous lability of blood pressure, original height of blood pressure, size of heart, and presence of arteriosclerosis or detectable renal injury.

Pain in the left chest was experienced by 2 patients who clinically did not have angina pectoris but whose electrocardiograms gave evidence of myocardial damage. No other subjective sensations were complained of by any member of the group.

Mechanism of the Epinephrin Response. In Table 1 the changes encountered in the blood pressure are compared with the changes in pulse rate. Fall in diastolic pressure was an almost uniform finding and occurred independently of rise or fall in pulse. Fourteen patients showed a rise in systolic blood pressure of 10 mm. or more. In 12 of them, the pulse rose 5 beats per minute or more. In only 1 was there a fall in the pulse rate of similar magnitude. In 17 patients responding by a fall in systolic pressure, only 8 showed a

rise in pulse rate, while in 7 the pulse was unchanged, and in 2 the rate fell. Apparently there existed a degree of parallelism between the changes in systolic pressure and in pulse rate such that a rise in pressure was quite uniformly accompanied by a rise in pulse rate, whereas in over half of those patients showing a fall in systolic pressure, the pulse was either unchanged or likewise fell. These findings are in accord with the conception originally stated by Bauer,[2] that two mechanisms are involved in the epinephrin reaction, namely, arteriolar dilatation causing a fall in diastolic pressure, and stimulation of the heart causing a rise in systolic pressure. Furthermore, Schulten *et al.*[5] have recently shown that following the injection of epinephrin there is an initial increase in venous return to the right heart (which hardly accords with the conception of arteriolar constriction), followed by a rise in systolic pressure and pulse rate, a pooling of blood in the lungs, and eventually an increase in cardiac output. This perhaps indicates that the cardiac stimulation is both active, as the direct result of the epinephrin itself, and passive, in response to increase in venous pressure. The vigor of response could well be altered by decrease in cardiac reserve which commonly accompanies long-standing hypertension. We suggest this as the explanation for the minimal response, as regards systolic pressure and pulse rate, encountered in so many of our patients. With this possible reservation, we were unable to convince ourselves that the cardiovascular response of our hypertensive patients to subcutaneously injected epinephrin differed in any consistent respect from the normal.

TABLE 1.—RELATION OF CHANGE IN BLOOD PRESSURE TO CHANGE IN PULSE RATE FOLLOWING SUBCUTANEOUS INJECTION OF EPINEPHRIN.

	No. of cases.	Pulse rises over 5.	Pulse falls over 5.	Pulse unchanged.
Rise, sys. pressure, 10 mm. or more	14	12	1	1
Fall, sys. pressure, 10 mm. or more	17	8	2	7
No change, sys. pressure	1	1	0	0
Rise, diast. pressure, 10 mm. or more	2	0	1	1
Fall, diast. pressure, 10 mm. or more	30	21	2	7
No change, diast. pressure	0	0	0	0

The Pituitrin Response. The response of the normal cardiovascular system to the intramuscular injection of pituitrin has recently been studied in detail by Moffat.[7] Contrary to widespread impression and to results obtained in animal experimentation, he observed only slight changes in blood pressure and pulse rate of 62 individuals observed over a period of 60 min. following injection. In general, there was a slight fall in pressure, affecting primarily the systolic, and a consequent decrease in pulse pressure. The pulse rate was not appreciably altered. In 3 individuals with hypertension, a pronounced fall in systolic pressure was observed.

With the exception of these 3 instances, we have not encountered

any study dealing with the cardiovascular response to the injection of pituitrin in arterial hypertension.

The average response exhibited by our group of 40 patients is expressed in Chart II. Five minutes after injection, there is an average rise in systolic pressure of 6 mm., and in diastolic of 4 mm. At 20 min., the diastolic pressure has risen 5 mm., near which level it remains throughout the observation period. From 20 to 40 min. the average systolic pressure falls gradually over a distance of 6 mm. after which it returns slowly toward the preinjection level. The average pulse pressure is slightly lessened during the period of systolic fall. The average pulse rate remains unchanged.

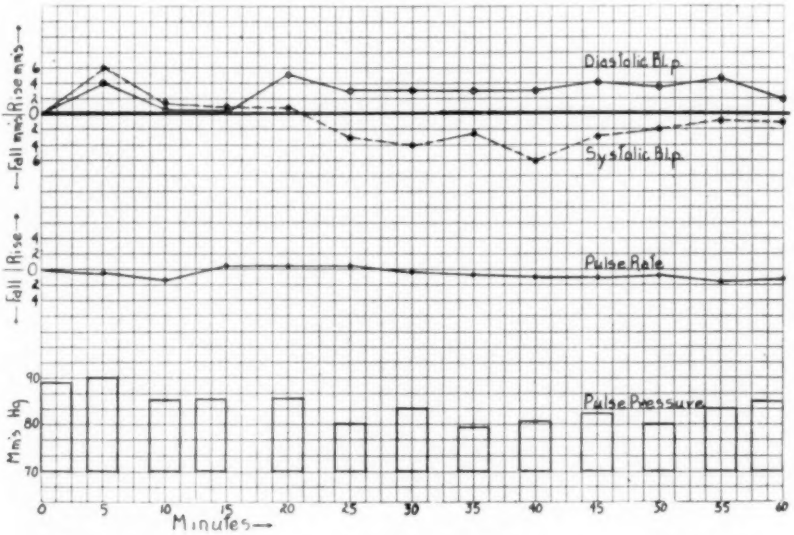

CHART II.—Average cardiovascular response to pituitrin of 40 persons with hypertension.

The individual changes exhibited by each patient were graphed in an effort to determine what effect the initial height of the blood pressure had upon the response. No consistent trend could be demonstrated. Those patients showing either a pronounced rise or fall were likewise studied to see if any clinical characteristic distinguished them as a group. None could be ascertained. The response of these same patients to epinephrin was likewise reëxamined wherever possible, to see if it differed by any consistent particular from that exhibited by the remainder of the group. These comparisons proved fruitless. We could not demonstrate that those patients showing a pronounced reaction to pituitrin injection were unduly vigorous or atypical in their epinephrin response.

It is evident that the cardiovascular response to pituitrin in our hypertensive series differed in no noteworthy respect from that obtained by Moffat in normal individuals. We are not even sure that the inconsequent fall in average systolic pressure and rise in average diastolic pressure observed in our series were due to pituitrin. It might be a chance reflection of the lability of blood pressure commonly encountered in hypertension patients when they are observed over a period of time. Since, however, Moffat obtained identical results in his patients, the conclusion is probably warranted that it was in fact a pituitrin effect.

Summary. 1. The blood pressure and pulse rate were measured at 5-minute intervals over a 60-minute period in 32 individuals with essential hypertension who had received a subcutaneous injection of 1 mg. of epinephrin.

2. The average systolic pressure fell slightly over a period of 35 min. and then returned to the preinjection level; the average diastolic pressure fell to a maximum low point at 45 min. and remained near that level throughout the remainder of the period. The average pulse pressure decreased. The average pulse rate rose.

3. A degree of parallelism existed between changes in the systolic pressure and in the pulse rate of these patients, such that a rise in pressure was usually accompanied by a rise in pulse rate, and a fall in systolic pressure by either a lowered or unchanged pulse. Elevation of systolic pressure may be primarily the result of cardiac stimulation by epinephrin, whereas the fall in diastolic pressure is attributable to arteriolar dilatation.

4. In 40 hypertensive patients studied in a similar manner after receiving a subcutaneous injection of pituitrin, a slight rise in average diastolic pressure and an equally slight fall in average systolic pressure, were observed after 20 min. The average pulse rate was unchanged.

5. In the same patient, an unusual response to the injection of pituitrin was not necessarily accompanied by a vigorous response to epinephrin.

6. No constant or frequent deviation from the reported normal cardiovascular response to the subcutaneous injection of epinephrin and pituitrin could be demonstrated in this series of patients with essential hypertension.

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MALIGNANT NEPHROSCLEROSIS (MALIGNANT HYPERTENSION).*

By H. E. MacMahon, M.D.,
PROFESSOR OF PATHOLOGY, TUFTS COLLEGE MEDICAL SCHOOL,
AND
J. H. Pratt, M.D.,
PROFESSOR OF CLINICAL MEDICINE, TUFTS COLLEGE MEDICAL SCHOOL
BOSTON, MASS.

Twenty years have passed since Volhard and Fahr used the term, "malignant nephrosclerosis," synonymously with malignant hypertension to designate a definite clinical and pathologic disease entity involving primarily the heart, blood vessels and kidney. Much has been written in Europe, but less in America, to substantiate the existence of such a disease. It is not possible in this very brief report to mention the names of all investigators who have shown interest in this condition, yet, since the problem is primarily a vascular one, it is a pleasure to acknowledge the debt which medicine owes to such men as Bright, Johnson, Gull and Sutton, Jores, Klotz, Hübner, Volhard and Fahr, and many others who have done such important work in the field of vascular pathology.

The present conception of the vascular lesions of the kidney held by clinicians and pathologists lacks both uniformity and clearness. There appear to be three rather distinct schools of thought: first, those clinicians and pathologists who recognize a granular or contracted kidney resulting from a primary disease of the small arteries and arterioles, and who use the terms, "chronic vascular nephritis," "arteriolosclerotic disease of the kidney," or "hypertensive nephritis," but who do not attempt to differentiate those cases which Volhard and Fahr would regard as malignant nephrosclerosis from cases belonging to the much more common disease which these same authors have called benign nephrosclerosis. The second group is much smaller and is comprised of those investigators who attempt to differentiate a benign from a malignant type of hypertension, but who simply regard malignant nephrosclerosis or malignant hypertension as a terminal phase, clinically and pathologically, of a preceding benign vascular disease. A third group believes that benign and malignant nephrosclerosis both from a clinical and pathologic standpoint may appear as two separate and distinct entities; that the malignant nephrosclerosis may become superimposed on a kidney already the seat of an advanced benign nephrosclerosis, but who believe, and this is important, that patients who have benign hypertension, even though it progress to renal

* Presented at the Meeting of The Association of American Physicians, Atlantic City, May 2, 1934.

decompensation, need never show the clinical and histologic changes characteristic of malignant nephrosclerosis. In other words, this third group, which constitutes rather a minority, believes that malignant nephrosclerosis may appear independently as a distinct entity, or that it may become superimposed on the benign disease.

Clinical Findings. The outstanding clinical findings of malignant nephrosclerosis are a gradually rising systolic and diastolic blood pressure which is maintained far above the normal level and which is usually higher than that of benign nephrosclerosis, and tends to be more constant than in the latter disease. Associated with this hypertension are signs and symptoms referable to the heart and blood vessels, particularly the blood vessels of the choroid and retina. The heart enlarges, headaches are severe and frequent, and visual disturbances are both common and serious, for "albuminuric retinitis" is extremely important and, as Volhard and Fahr, in 1914, pointed out, it may be the earliest sign of diagnostic importance in differentiating malignant from benign nephrosclerosis. As the disease progresses the picture changes from what was primarily a cardiovascular disease to one in which the kidney changes appear to play the leading rôle. These renal signs and symptoms may appear in an acute, a subacute or chronic form, and are characterized primarily by an increasing tendency toward fixation of the specific gravity at a level of 1.010 to 1.012 (isosthenuria), a polyuria that is finally replaced by oliguria, the presence of a considerable amount of albumin, a variety of casts and the almost constant presence of red blood cells in the urine. As the disease advances there appear other signs of renal insufficiency, with an elevation of the non-protein nitrogen constituents in the blood and the presence of positive indican and xanthoprotein reactions in the urine. There is in addition increased pallor, anemia, loss of appetite, and loss of weight. If the patient does not die prematurely from cardiac or vascular disease, the end will come with uremia. Indeed, in the late stages the clinical picture is indistinguishable from that of chronic glomerulonephritis, a fact which is substantiated by autopsy records which show that approximately 65% of these patients with malignant nephrosclerosis die a uremic death. It is interesting at this point to mention that edema which is so often a striking feature of chronic glomerulonephritis is, in malignant nephrosclerosis, usually absent, and if present is almost invariably of cardiac origin. This disease is seen, as a rule, in middle-aged individuals. In 60 cases which came to autopsy the average length of life was 42 years, and of this group, females were more numerous than males.

The sequence of events in malignant nephrosclerosis, in which a cardiovascular disease appearing in younger people progresses rapidly, terminating fatally by a uremic death, and seldom running a course of more than 2 to 4 years, forms a sharp contrast to the long slow chronic course of benign nephrosclerosis seen in elderly people

in whom death most commonly occurs after a period of years through myocardial or cerebral injury.

Benign nephrosclerosis portrays itself throughout its long and chronic course as primarily a disease involving the heart and blood vessels, while any signs or symptoms referable to disturbances in kidney function stand far in the background. There is frequently substernal pressure or shortness of breath on exertion and in the later stages evidence of chronic passive congestion of the lungs, liver and kidneys with or without subcutaneous edema. The cerebral signs and symptoms vary from mild headaches, dizziness, throbbing, slight visual disturbances and confusion, weariness and failing memory, to the more severe cerebral accidents resulting from thrombosis or hemorrhage. The course is remarkably slow, and for years the patient may present no symptoms attributable to his disease or may suffer recurrent cardiac weakness. The skin is often flushed and an examination of the blood may show the red blood cells in excess of the normal. In some measure it is a disease which responds to treatment. The first danger is the heart; the second the vessels, either coronary or cerebral, and the third danger is a pulmonary complication such as bronchopneumonia. The urine shows little change in color, volume or concentration. Albumin and an abnormal sediment are usually lacking. In only 2 of 100 cases did the vascular lesion advance to such a degree as to suggest a true renal insufficiency. This benign nephrosclerosis is seen most commonly in patients above 50 years of age. In a consecutive series of 100 patients who came to autopsy, collected by one of us (H. E. M.), the ages varied from 40 to 80 years, the largest group falling between 60 and 70.

Anatomic Findings. The findings at the autopsy table in a patient dying of malignant nephrosclerosis may vary considerably, depending on whether the patient dies in the early stages of the disease from myocardial injury, cerebral injury, rupture of the aorta, or a complicating pneumonia, or whether the patient dies in the late stage with all the clinical signs of uremia. Of the 60 patients who came to autopsy, 35 died of uremia, many showing the classic changes with pericarditis, pharyngitis, gastro-enterocolitis, edema of the brain and lungs, and a uremic odor to all tissues. Twelve of the patients showed extensive cerebral hemorrhage, 10 died of heart failure, 2 of aortic rupture and others of pneumonia, erysipelas and septicemia. There was nothing distinctive about the habitus, although the majority were large-boned individuals varying greatly in weight. The external pallor so often recorded by the clinic corresponds to a diminution in the quantity of blood. The two organs showing the most striking changes, and the changes most valuable from a diagnostic standpoint, are the heart and kidney. The heart in this series of cases had an average weight of nearly 600 gm., the left ventricle showing a most remarkable concentric

form of hypertrophy. The kidney is usually of about normal size. It may be slightly reduced and finely granular, but more striking than the alteration in size of this organ is the congestion of both cortex and medulla and the presence of petechial hemorrhages, not only throughout the kidney, but also beneath the epithelium of the kidney pelvis.

The findings at the postmortem of patients dying with benign nephrosclerosis may be equally variable, but signs of uremia, if they do occur, are extremely uncommon. Usually in this benign nephrosclerosis there is a plethora and, while the heart and kidneys may somewhat resemble those from a patient with malignant nephrosclerosis, petechial hemorrhages within the kidney are absent. Actually, the difficulty in the differential diagnosis of far-advanced malignant nephrosclerosis is not one between this disease and the benign nephrosclerosis, but rather one between malignant nephrosclerosis and chronic glomerulonephritis. Patients with chronic glomerulonephritis will usually show a moderate hypertrophy of the left ventricle, but this is seldom to be compared to the extraordinary hypertrophy seen in malignant nephrosclerosis. It is only fair to state that if one is doing an autopsy and knows nothing at all of the preceding clinical history, it could well be impossible, from the gross anatomic standpoint alone, to differentiate a case of chronic glomerulonephritis from one of chronic malignant nephrosclerosis, since the pallor, the anemia, the signs of uremia, the hypertrophy of the left ventricle and the granular kidney showing petechial hemorrhages are common to both.

Microscopic Findings. The most important histologic changes in malignant nephrosclerosis are found in blood vessels, including the medium-sized muscular arteries, the small arteries and the arterioles. They are found throughout the body, but the most marked lesions are seen in the arterial tree of the kidney, and also, though to a lesser degree, in the vessels of the pancreas, capsule of the adrenal, gastro-intestinal tract, spleen, brain and fundus of the eye. There is not simply a single change in these vessels, but a variety of changes. There is hypertrophy of the vessels with marked thickening of the media and dilatation of the lumina of the larger of these vessels. This is often accompanied by a reduplication of the internal elastic lamina, and an increase in the connective tissue of the intima and adventitia (Fig. 1). In the smaller arteries and arterioles a fluid mucoid material accumulates beneath the endothelium which may increase to such a degree as to bring about apparent occlusion of the lumen. The endothelial cells of vessels showing this change are usually swollen, and occasionally a substance is seen within the cytoplasm that takes the same tinctorial reaction as the subendothelial mucoid material of the intima. The endothelial cells proliferate and enlarge, and become incorporated in this underlying ground substance (Fig. 2). Where the lesion is

older, an organizing process is seen within the thickened intima, fibrils appear within this amorphous ground substance and cells beneath the endothelium increase in number, become drawn out as spindle-like forms and arrange themselves in concentric layers separated by collagen fibrils (Fig. 3). This picture has been given a variety of names, as "fibrosis of the intima," "endarteritis obliterans" and simply "intimal swelling." It may undergo regressive changes in the form of hyaline transformation, or may show con-

FIG. 1.—Interlobar artery from the kidney of a patient, aged 33 years, dying of malignant nephrosclerosis. Note the extraordinary vascular hypertrophy with the greatly thickened media, and the reduplication of the internal elastic lamina. A small branch, also showing medial hypertrophy, is seen at one side.

siderable lipoid material, which is taken up by cells which accumulate in rows and clusters beneath the endothelium. The outcome of these changes leads to a narrowing of the lumen which far too commonly produces an apparent complete occlusion, a change which is frequently assisted by thrombosis of the lumen (Fig. 4). Another change found within the smaller arteries and arterioles in malignant nephrosclerosis, and quite the most spectacular lesion of the disease, is the marked destruction of the entire wall, with fragmentation of

the basement membrane, a separation and splitting of the layers of the vessel wall resembling a dissecting aneurysm, a saturation of the wall with red blood cells, plasma and fibrin, necrosis of muscle fibers and hemorrhage into the surrounding stroma (Fig. 5).

In the kidney these vascular lesions appear most clearly, and occur most commonly in the small lobular arteries and afferent vessels to the glomeruli. These hemorrhagic lesions of the vessels

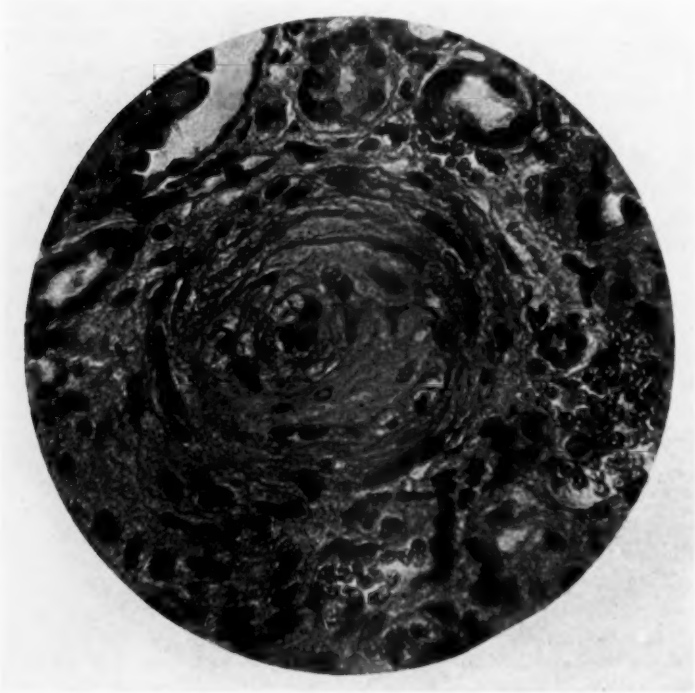

FIG. 2.—Small lobular artery of the kidney. The lumen is apparently obliterated through the extraordinary change in the intima. The intima is greatly thickened by the deposition of a mucoid ground substance containing few large ovoid cells, resembling the swollen endothelial cells at the center. In the more peripheral portion of this intimal thickening the cells appear spindle shaped and are separated by collagen fibrils. The muscular fibers of the media are replaced by connective tissue and ground substance.

are not merely a terminal event, for these are found in all stages of repair. Endothelial cells and adventitial cells, proliferating and building intercellular fibrils and ground substance often assume a nodular form which has been described as resembling a small granuloma. All of these changes described as occurring within the arterioles may be found within the capillary tuft of the glomerulus as well (Figs. 6, 7, 8 and 9). Very commonly one may trace the

changes in the wall of an afferent arteriole directly over into part or all of the capillary tuft of the glomerulus; and the glomerulus, like the arteriole, may show chronic, fresh, healing, healed and even recurrent lesions. The tubules of the kidney instead of undergoing simple atrophy and collapse may show varying types of degeneration and even necrosis (Fig. 10), and the contents of the tubule may vary from precipitated protein, fibrin, red blood cells, desquamated epithelial cells and polymorphonuclear leukocytes to

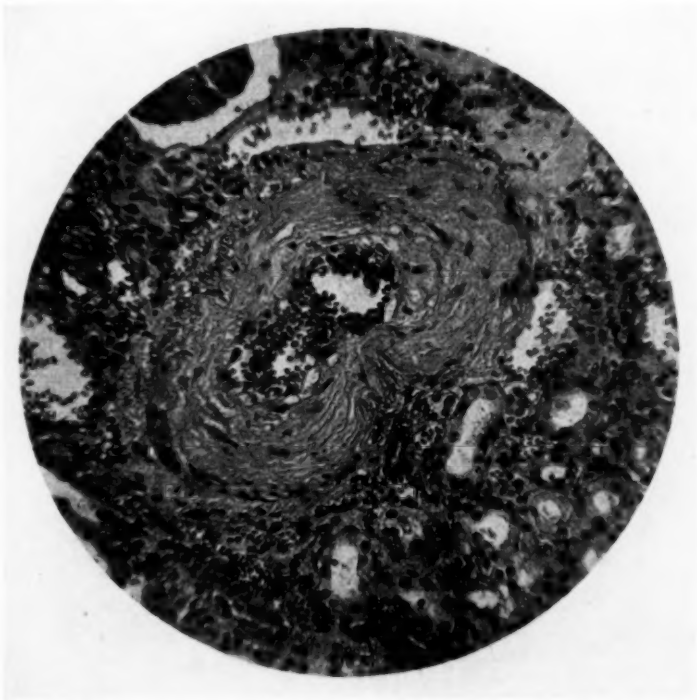

FIG. 3.—Lobular artery of the kidney. It is greatly increased in size. The muscular fibers of the media are hypertrophied and form a narrow outer border. Most striking is the marked thickening of the intima by a mucoid type of ground substance containing few cells and scattered intercellular fibrils. There is no increase in elastic tissue in the intima in this vessel.

little or nothing at all. This destruction of tubules may be very widespread and the remainder may show marked compensatory hypertrophy. In addition to these vascular, glomerular and tubular changes, the stroma of the kidney becomes greatly increased and shows signs of a chronic resorptive inflammatory reaction with foci of lymphocytes and mononuclear cells which are usually grouped in foci.

Mention has already been made of the difficulty the clinician

may have in differentiating benign from malignant nephrosclerosis during the early phase of the disease, and of the similarity at this stage in the anatomic changes seen in these two diseases at the autopsy table. Therefore, it might be well at this point to contrast briefly the histologic changes in the vessels in malignant nephrosclerosis with those of the benign disease. The localization of the vascular lesions in both diseases is the same; furthermore, the changes in the small muscular arteries which show medial hyper-

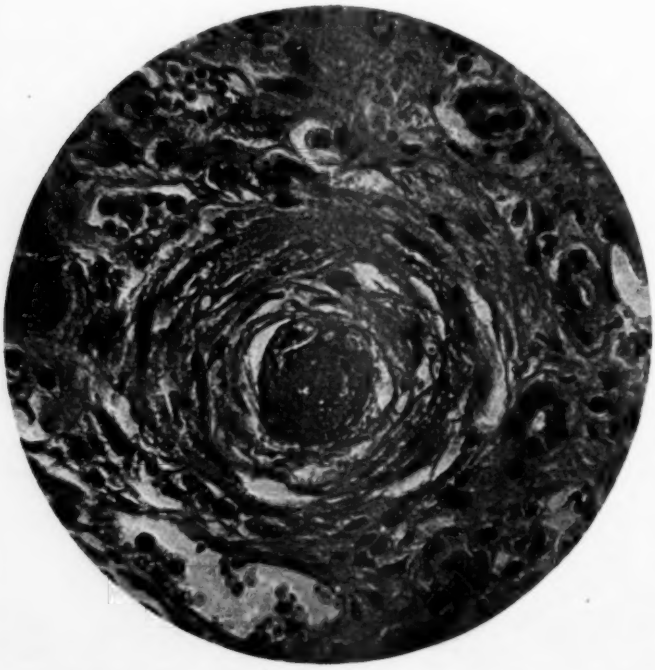

FIG. 4.—A lobular artery of the kidney. The normal architecture of the vessel wall is replaced by concentric layers of spindle cells and intercellular collagen fibrils embedded in ground substance. The endothelial cells are not visible and the lumen is occluded by a small fibrin thrombus.

trophy, intimal elastosis and connective-tissue thickening of the adventitia, are in the two diseases indistinguishable, but with this the similarity of the two diseases ceases, for in the smaller arteries and arterioles of the size of the lobular and afferent vessels of the kidney, the changes in the two diseases present a striking contrast. In benign nephrosclerosis the most constant findings comprise a swelling of the basement membrane of the arterioles which may show lipoid degeneration, and a replacement of the muscular fibers of the media by connective-tissue cells and ground substance. The

lumen of the smallest vessels is somewhat reduced and the wall would appear to have lost its ability, not alone to relax and dilate, but also to undergo any involuntary contraction. In the kidney this swelling of the basement membrane and, to a less extent, the increase in ground substance in the wall of the arteriole may be traced to the glomerulus, to the glomerulus capsule and to the tubule as well. It is common to find scattered glomeruli that have collapsed and appear as eosin-staining nodules of hyaline material.

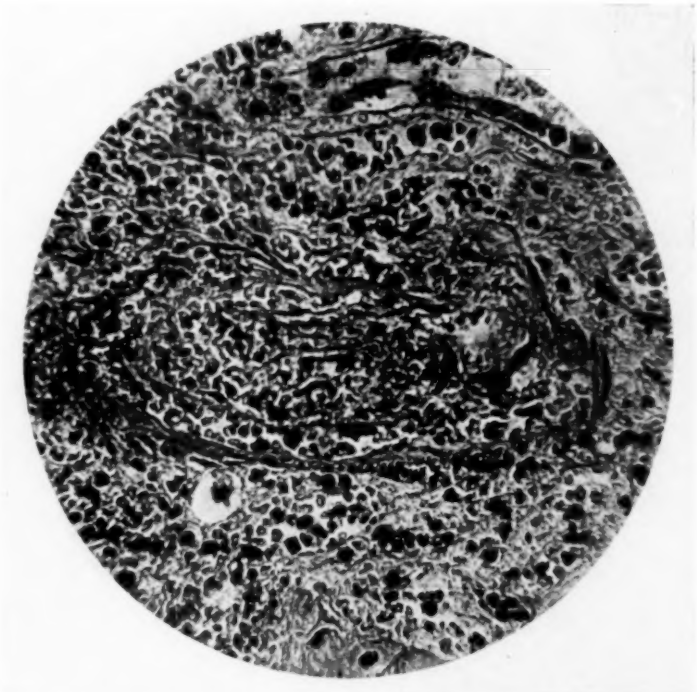

FIG. 5.—A small lobular artery of the kidney. The vessel is scarcely distinguishable through the extensive destruction of the wall. The lumen is distended with red blood cells. The walls of the vessel are broken and separated by plasma and red blood cells. There is a fresh hemorrhage into the surrounding stroma.

The corresponding tubule, even before the glomerulus shows any appreciable change, may be quite small, shrunken and collapsed. In malignant nephrosclerosis the arterioles may show all of these changes, but in addition there is the accumulation of mucoid material in the intima (Fig. 2), the endarteritis (Fig. 4) and the hemorrhage and necrosis of the wall (Fig. 5). The destructive and inflammatory lesions of the glomeruli (Figs. 6, 7, 8 and 9), tubules (Fig. 10) and stroma seen in malignant nephrosclerosis also aid in the differential diagnosis.

Since it has also been pointed out that in the late stage malignant nephrosclerosis, clinically and in the postmortem room, may simulate chronic glomerulonephritis, it is in order here to state briefly the differential points in the pathologic histology, especially within the kidney, of these two diseases. The most important lesion from the standpoint of a differential diagnosis is the change within the glomerulus. In a typical well-advanced case of chronic glomerulonephritis as many as 90% of the persisting glomeruli show varying

FIG. 6.—Glomerulus, showing a fresh and severe lesion in malignant nephrosclerosis. The glomerulus is large and many of the capillaries of the glomerular tuft are overdistended with blood. There is rupture of the basement membrane and hemorrhage into the capsular space and proximal convoluted tubule.

stages of an inflammatory reaction, whereas in malignant nephrosclerosis an equally large percentage is usually relatively intact, and shows little more than a slight increase in the size, in the number of cells and in the ground substance. The remaining 10% may show hemorrhages, degeneration, inflammation and repair. The changes in the arteries and arterioles of the kidney in chronic glomerulonephritis vary to an extreme degree—on the one hand are cases in which the vascular tree is unchanged, and on the other

hand are cases in which the vascular lesions are identical with those of malignant nephrosclerosis, including the medial hypertrophy, the lamellar elastosis, the mucoid degeneration of the intima, the endarteritis obliterans and, finally, hemorrhage, destruction and thrombosis of the wall. In general, however, the vascular lesions within the kidney in glomerulonephritis, in contrast to malignant nephrosclerosis, play a relatively unimportant rôle. Much more

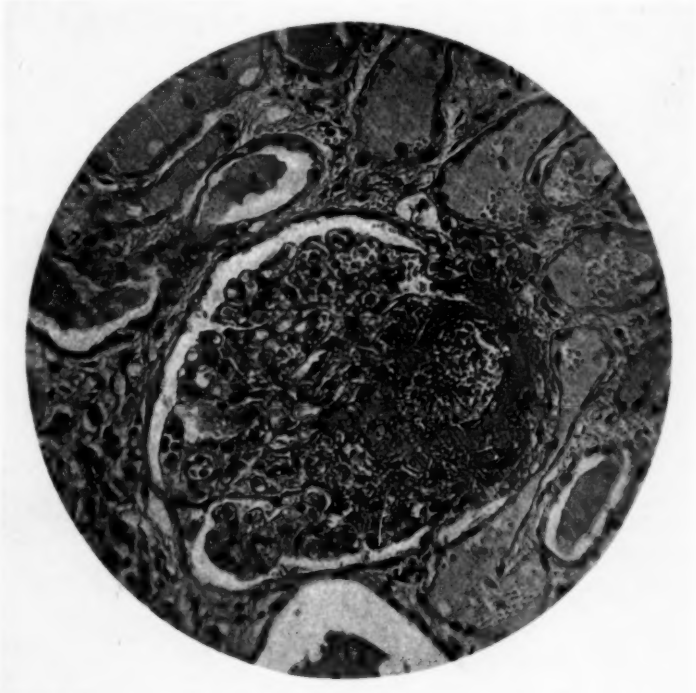

FIG. 7.—Glomerulus, in malignant nephrosclerosis, showing an older lesion than Fig. 6. There is marked dilatation of the afferent arteriole as it enters the glomerulus. The lumen of the vessels is partially thrombosed. The wall is saturated with fibrin which lies between the damaged endothelium and the stretched and fragmented basement membrane. The capillaries of the tuft are thickened by an accumulation of ground substance beneath the endothelium. While some capillaries are obliterated, others are distended with blood.

important in this consideration than the character of the lesion is a comparison of the distribution and localization of the vascular lesions in these two diseases. In glomerulonephritis the changes affecting the smaller vessels are limited in general to the kidney, and especially to the afferent vessels leading to injured glomeruli, whereas in malignant nephrosclerosis the vascular lesions are very widely spread, not only throughout the kidney, but throughout the

body as well. In the tubules one finds little that is helpful in the differential diagnosis, as the destruction and hypertrophy in both diseases may be the same. Just as glomerulonephritis may appear as an acute, a subacute or chronic disease, so may malignant nephrosclerosis show the same diversity in histologic findings.

A typical case of malignant nephrosclerosis, or benign nephrosclerosis, or chronic glomerulonephritis will offer little difficulty

FIG. 8.—Glomerulus, showing a still later stage than Fig. 7. There is still some residual fibrin in the wall of the afferent arteriole and within the structure of the glomerulus. Note the proliferation of epithelial cells of the capsule forming a narrow crescent.

clinically, at the autopsy table, or histologically in establishing a diagnosis; but it is the experience of all investigators who have made a study of these diseases that Nature does not classify as sharply and as clearly as man might wish, for one finds transitions between these diseases. The appearance of transitional forms in no way contradicts the statement that all three should be considered as separate diseases, any more than their occurrence is to be looked upon as evidence that all are different stages of the same disease.

Etiology. From the standpoint of etiology there are two questions to be answered. The first is: how is one to explain these histologic changes in malignant nephrosclerosis? The second is; what is the primary cause of the disease itself? To answer the first of these questions, which involves the histogenesis of the vascular lesions, several hypotheses have been advanced. The earliest of these, and the explanation given by Fahr, assumes the presence of a toxin which directly injures the vessel wall and leads to necrosis and an

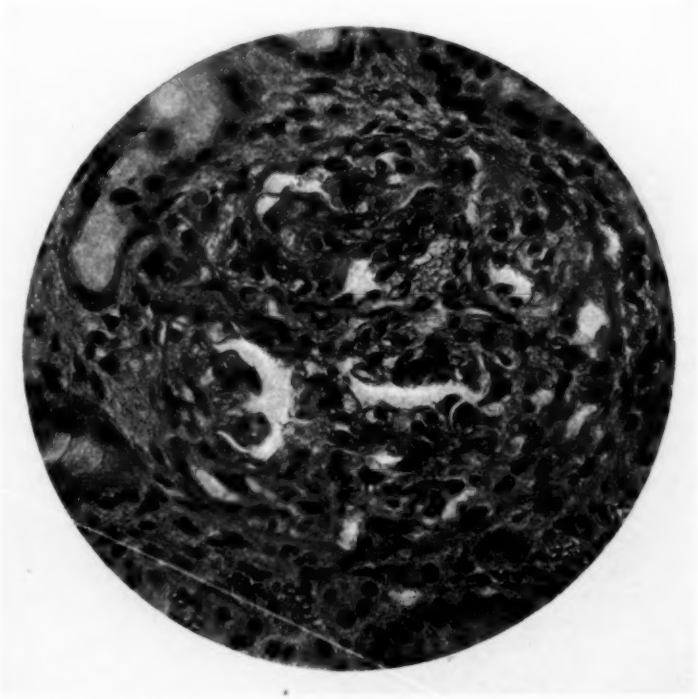

FIG. 9.—Glomerulus, showing an even later stage than Fig. 8. The capillaries of the tuft are collapsed and ischemic. The epithelial cells covering the capillaries are increased in size and number. There are adhesions between the tuft and the greatly thickened layer of capsular epithelium which forms an easily recognizable crescent.

inflammatory change. A second hypothesis, and one suggested by Volhard, considers the lesions to be the end result of prolonged ischemia through contraction of the larger arteries. A third and more recent attempt has been made to explain the changes on the basis of Ricker's observations bearing on the variability in contractility of different portions of the vascular tree. It was assumed that a stimulus sufficient to cause contraction of one segment of a vessel would lead to paralysis and dilatation of the smaller vessels

beyond, and this, if continued, would ultimately lead to changes in the vessel wall and even to necrosis and hemorrhage. The most recent attempt at an explanation is that of Schürmann and MacMahon, who consider that an injury to the endothelium, which may be very slight or very marked, is really the first and most important change. The endothelium constitutes a barrier between the blood and the tissue fluid and, when this is injured, substances from the blood may pass into the vessel wall. The quantity and quality

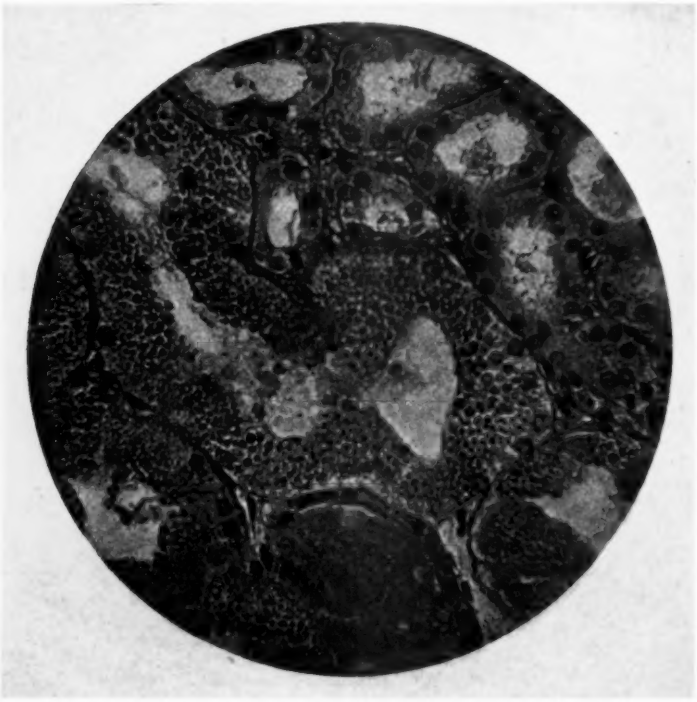

FIG. 10.—A small group of tubules from the kidney of a patient dying with malignant nephrosclerosis. The most striking change here is the droplet degeneration of the epithelium bordering the tubules.

of these substances vary with the degree of injury. If the damage is slight, these substances may be simply of a fluid nature; if, on the other hand, the damage is great and the endothelium itself is destroyed, then not only may fluids pass into the wall, but also the cellular elements. The change in the blood is almost immediate coagulation, whereas the change in the wall varies from a mucoid degeneration of the intima to fragmentation and necrosis.

In an attempt to answer the second question—namely, what is the cause of the disease itself—we have studied the clinical histories

of 60 patients who died of malignant nephrosclerosis. There seemed no constant relationship to past disease, to race, to sex or to occupation that was of great importance. Occasionally there was a story of lead poisoning, and diphtheria appeared in 2 cases shortly before the onset of hypertension. Syphilis, including prolonged mercurial treatment, has also been reported by Fahr. In addition to these external factors in the etiology, comes the probable association of some cases with disturbance in endocrine activity. There are certain cases of pituitary basophilism associated with basophilic adenoma of the pituitary, and also cases of cortical tumors of the adrenal which clinically and pathologically show malignant nephrosclerosis. Lastly, there are those cases of malignant nephrosclerosis appearing in young women, the subjects of repeated toxemias of pregnancy. This apparent lack of any one constant exogenous or endogenous factor in the etiology of this disease seems to strengthen the impression that the constitutional factor, including the age of an individual and familial or individual tendencies, plays a very important part.

Summary. Malignant nephrosclerosis from both a clinical and pathologic standpoint should not be looked upon as merely a progression of benign nephrosclerosis, but rather as a distinct and separate disease. It may occur alone or as a terminal complication of the benign disease. In the very early stages, when only the cardiovascular signs and symptoms are present, it may be impossible not only to say whether one is dealing with an early case of benign or malignant nephrosclerosis, but also it may be equally impossible to predict into which of these diseases the case will ultimately fall. As the disease progresses, the renal component becomes more and more conspicuous, and in the late stages it may be impossible to differentiate this disease from chronic glomerulonephritis. The etiology of benign and malignant nephrosclerosis has probably much in common, for one sees cases of chronic lead poisoning, pituitary basophilism, toxemias of pregnancy and so on, which on the one hand may show benign nephrosclerosis and on the other the much less frequent malignant disease. The course and prognosis depend not alone on the quality and quantity of the exciting agent but also in the manner in which the vessel wall responds. Where the response is of a simple degenerative nature, the disease progresses slowly, the prognosis is good and such cases are classed as benign nephrosclerosis. Where the vascular response is characterized by inflammatory changes of the intima, necrosis and hemorrhage, the course is more rapid, the prognosis is poor, and such cases are classed as malignant nephrosclerosis.

NOTE.—For a complete bibliography see Fahr, T., *in* Handbuch der speziellen pathologischen Anatomie und Histologie, Henke and Lubarsch, Berlin, Julius Springer, vol. **6**, Pt. 1, 1925; vol. **6**, Pt. 2, 1934.

PARADOXICAL EMBOLISM.

By Frank J. Hirschboeck, M.D.,
DULUTH, MINN.

(From the Department of Medicine, Duluth Clinic.)

Although embolic phenomenon had been described in the 18th century and in the early part of the 19th century, the pathogenesis of embolism was not accurately observed until Virchow published his observations in 1856, which remain a model of scientific anatomic, experimental and clinical research. Equally important are Cohn's[1] book published in 1860 and the writings of Cohnheim in 1877.[2] Pulmonary and cerebral embolism now so frequently recognized and well understood were then for the first time clearly appreciated.

Emboli in the general systemic circulation supply an interesting subgroup in the consideration of embolism in general. They are derived directly from thrombi in the left heart associated with heart failure or disease of the mitral or aortic valves, and more rarely from thrombi in the aorta and large arteries, or from the pulmonary veins as a result of pulmonary lesions, such as pneumonia, abscess and gangrene, tuberculosis or tumors.

A small but distinctive group arises in association with thrombosis in the systemic veins and embolism in the general systemic circulation. In these instances the embolus passes from the right auricle to the left auricle through a patent foramen ovale, or, very rarely, through a patent interventricular septum, as reported by Louis, and has been termed a "paradoxical" (Zahn[3]) or "crossed" (Rostan[4]) embolism. Cohnheim demonstrated the first instance in 1877, observing an embolism of the right middle cerebral artery in a case of widely patent foramen ovale and with thrombosis in the veins of the lower extremities. Zahn, in 1881, reported the first necropsy finding of an embolus in transit, as it were, through a persistent foramen ovale. In 1888, Hauser[5] made a similar observation. Barnard,[6] reporting another instance of an embolus lodged in the patent foramen ovale in 1930, cited a total of 8 such instances in the literature up to that time.

The passage of tumor emboli is naturally very rare, but Zahn[7] reported an instance in 1889, in which there was evidence of the passage of a tumor fragment through a patent foramen ovale. In regard to the systemic circulation, it is certain that tumor cells and septic or infective emboli must necessarily be able to traverse the pulmonary capillaries without leaving evidence of pulmonary disease. It is therefore doubtful whether tumor formation or infec-

tive emboli carried through the systemic circulation necessitate any consideration of a patent foramen ovale as a route of transportation, except in the rarest instances.

About 50% of the instances of paradoxical embolism are associated with antecedent pulmonary embolism. A study of the intraäuricular blood pressure establishes the pressure as somewhat higher in the left auricle than in the right, assuring competence as far as any circulation of blood from the right auricle to the left auricle is concerned in a state of health. An anatomic patency is therefore associated with a physiologic competence. Any disturbance in the pressure relationship may favor the development of paradoxical emboli when thrombosis in the venous circulation is present. Haggart and Walker[8] experimentally showed that a sudden occlusion of the left pulmonary artery caused an immediate rise in the pulmonary pressure of about 29%, whereas with total pulmonary occlusion the pressure increased rapidly by 120 to 257% with an immediate fall in the systemic arterial pressure.

Parkinson[9] reported an interesting instance of a patient who developed pulmonary infarction from an embolism during the convalescence from an operation. The patient improved for 3 weeks and then died suddenly following an attack of breathlessness. At autopsy the right ventricle was found to be dilated and showed some degree of hypertrophy, indicating to the observer that a condition of increased pressure in the pulmonary circulation had existed since the first infarction 3 weeks previously. The patient had a patent foramen ovale only 0.3 cm. in diameter and embolism of the paradoxical type had not occurred. Hence, though a foramen ovale may be present, paradoxical emboli do not necessarily occur with increased pressure in the right side of the heart, but the predisposition thereto must nevertheless be held in mind. The anatomic evidences of increased right ventricular pressure, because of the pulmonary infarction, however, were conclusive.

Patency of the foramen ovale is the commonest of all fetal relics. The literature generally recognizes the incidence of patency in all necropsies as between 30 and 35%. The uniformity of this percentage in the literature is striking.

It would appear from the literature that the size of the patency makes a great difference. In 1100 necropsies observed by Thompson and Evans[10] there were 319 instances of patent foramen ovale in which the opening was only large enough to admit a probe. In 67 (6%) of the total necropsies, a pencil could be admitted into the orifice. The writers conclude that it is essential that over one-third of the pulmonary circulation be depleted by pulmonary embolism to favor the establishment of a paradoxical embolus. If 50% or more of the pulmonary circulation is cut off suddenly by an embolus, death results within 10 to 30 min. Also, when pulmonary embol-

ism results, sufficiently extensive to raise the pressure in the right side of the heart and yet not so extensive as to produce sudden death, a further embolus must arrive in the right auricle from the venous system to produce a paradoxical embolus, necessarily a reduced and rare coincidence. If the embolus represents a cast of the lumen of one of the larger systemic veins, a foramen ovale must be patent to a size commensurate with the passage of an embolus of such size. The rarity of the condition can thus be appreciated and probably accounts for the scarcity of any articles in the literature. Death, evidently, not uncommonly ensues if the newly arrived embolus becomes lodged in the foramen, as the 9 reported cases show.

Diagnostically, paradoxical embolism may be assumed as occurring in life if the patient is the subject of venous thrombosis, develops an embolus in the systemic circulation and, after a careful search, has no other apparent causes for arterial embolism. If pulmonary infarction precedes the embolic accident, the diagnosis is more certain.

Case Report. Mrs. M., aged 74, a widow, domestic by occupation, entered St. Mary's Hospital April 16, 1934, and died April 30, 1934, under the care of Dr. R. M. Mayne.

Present complaint is acute pain in the right lower quadrant of the abdomen associated with hernia and accompanied by vomiting. This pain began at 7 P.M., April 16, 1934. There had been several previous attacks of hernial strangulation in the right lower quadrant reduced by a nurse at the Home where she resided, but this time the effort proved unsuccessful.

Physical Examination. The patient was well developed, well nourished. Examination of the head and neck was negative. The chest examination was normal except that there was a blood pressure of 170 systolic, 80 diastolic with a slight heart enlargement. However, the sounds indicated no abnormality. The abdominal examination was negative except for the strangulated hernia. The urine was normal, with occasional red blood cells. The patient was operated upon by Drs. W. G. Strobel and R. M. Mayne at 11.55 P.M., April 16, 1934. A sac containing small bowel and omentum was found, with the bowel apparently gangrenous for about 6 inches of its length. Two ileostomy tubes were inserted and the ileum exteriorized, but at the time of closure the ileum was dropped back into the abdomen with the tubes *in situ*, as the color of the loop apparently had been restored. The operation was performed under spinal and gas-ether anesthesia.

On April 17 the patient had an oxygen tent used and nasal decompression begun. The condition was good, but the postoperative temperature was 102.4° F., no doubt due to the septic factor. On the 18th the temperature was 101°. On April 21 the patient appeared to be quite well except for some disorientation, temperature 102°. On April 22 it was found that the dressing was soaked with fecal matter and evidently a fecal fistula had formed. Temperature was 102.° The face was rather drawn. On April 29, at midnight, the patient had rapid respiration, with the pulse regular, but the general appearance was very bad. Temperature 102°. Breathing became very shallow and the patient died at 12.35 A.M., April 30.

The postmortem performed by Dr. George Berdez at 2 P.M., April 30, 1934, revealed the following essential data: (1) Some edema of the ankles, especially on the right side. (2) An enterostomy wound with a fecal fistula and escape of gray-greenish mucous material. The peritoneal cavity

contained no exudate and the serosa was smooth. Beginning gangrene of a loop of the small intestine about 1½ feet above the iliocecal valve. (3) The pulmonary artery contained a large twisted embolus measuring 0.9 cm. in diameter. (4) The heart contained some partially clotted blood. The foramen ovale was patent to the size of a pencil and a large embolus was caught passing from the right into the left auricle through the foramen. An embolus measuring about 3 cm. in length had entered the cavity of the left auricle, but was firmly caught in the foramen by its proximal end. The pathologist thought the embolus to represent a cast of the iliac or femoral vein. The heart weighed 370 gm. The coronary arteries showed arteriosclerosis Grade II, the myocardium showing a few small areas of fibrosis. The mitral and aortic valves were slightly thickened. Left lung weighed 280 gm. The right lung weighed 380 gm. In the posterior part of both lower lobes there was an area of congestion and atelectasis. Several small recent pulmonary emboli in the branches of the pulmonary artery, especially in those leading to the atelectatic areas. The bronchi contained little mucous material. (5) Spleen normal. Kidneys slightly irregularly granular. The capsules somewhat adherent. A serous cyst 3.5 cm. in diameter in the upper part of the left kidney. Liver weighed 1150 gm. Gall bladder slightly thickened and fibrous. Bile ducts patent. Pancreas normal; stomach normal. Intestines normal except for the area about the site of the operation.

Anatomic Diagnoses. (1) Massive pulmonary embolus; (2) patent foramen ovale, embolism in the patent foramen ovale; (3) partial atelectasis of the lower lobes of both lungs; (4) calcified hilus glands; (5) solitary serous cyst of the left kidney; (6) arteriosclerotic kidney; (7) arteriosclerosis Grade II of the aorta; (8) edema of the ankles, especially the right; (9) status after enterostomy.

Summary. 1. The question of paradoxical embolus and its incidence is discussed because of its rarity and the paucity of articles on the subject in the American literature.

2. Reference is made to the occurrence of emboli lodged in the foramen ovale at the time of death and the mode of production of paradoxical emboli considered.

3. The case report is illustrative of the sequence of paradoxical emboli in the systemic circulation subsequent to venous thrombosis and in association with antecedent pulmonary embolism. It represents one of the rare instances in which an embolus is found "in transit" through the patent foramen ovale at the time of death.

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METASTATIC MELANOCARCINOMA WITH APPARENT RECOVERY.*

By Joseph Jordan Eller, M.D.,
ASSISTANT PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY,
AND
Irving L. Schonberg, M.D.,
CLINICAL ASSISTANT OF THE DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, NEW YORK POST-GRADUATE MEDICAL SCHOOL, NEW YORK CITY.

(From the Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital of Columbia University.)

The following case of microscopically proven, rapidly growing melanoma is herein reported, because of its unusual clinical course and favorable response to therapy.

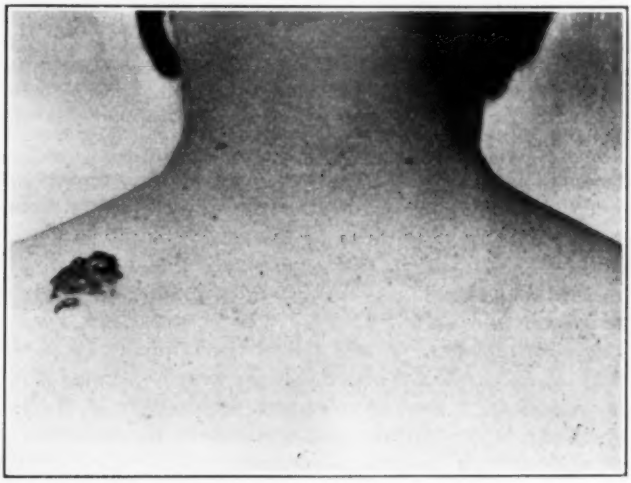

Fig. 1.—Melanocarcinoma developing in an irritated blue-black mole, May 8, 1929.

Since Laennec first described melanoma in the human in 1806, there has been much controversy regarding the genesis and treatment of this condition. Some clinicians believe that this condition should be left untreated; others that various methods, such as Roentgen rays, radium and surgery should be instituted. Cases have been reported without recurrence in which different methods

* Published by courtesy of Dr. R. Franklin Carter from the Surgical Department of New York Post-Graduate Medical School and Hospital; from the Dermatological Department of New York Post-Graduate Medical School and Hospital, Dr. George M. MacKee, Director.

of therapy had been employed. In any event the progress of different cases may vary greatly.

The following is a case of melanocarcinoma of the skin of the back with metastasis in the supraclavicular space. It had grown rapidly in the month preceding operation. Treated radically by surgery,

FIG. 2.—Extent of excision. In spite of this lymphatic metastases occurred. Operated July 19, 1929.

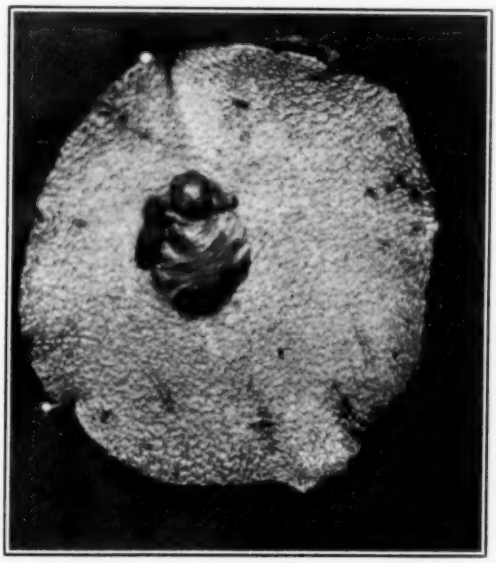

FIG. 3 —Tissue removed from back, July 19, 1929.

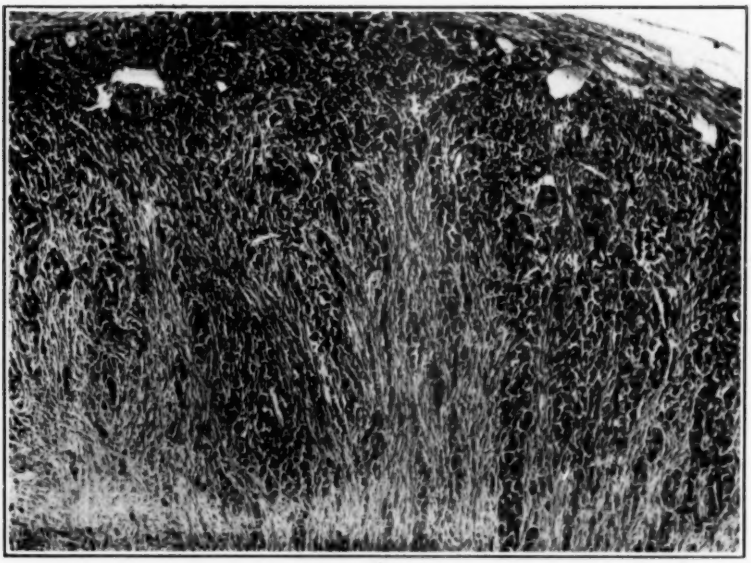

FIG. 4.—Microscopic section of metastatic gland.

FIG. 5.—Postoperative, January 6, 1934.

Roentgen ray, and radium therapy, it has shown no recurrence 4½ years after treatment.

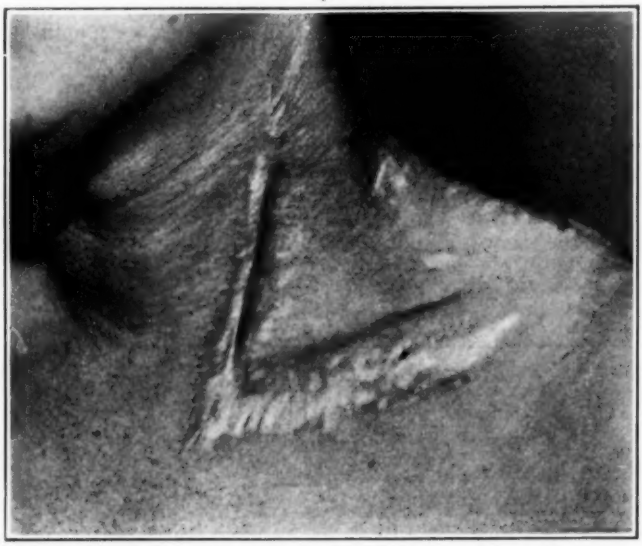

FIG. 6.—V-shaped exposure for removal of glands after closure.

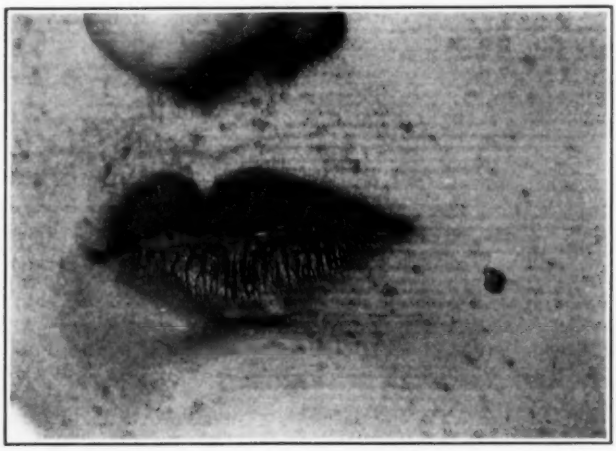

FIG. 7.—Preoperative. Melanoma on left cheek, June 16, 1929.

Case History. The patient, a female, aged 19 years, had always enjoyed good health. In 1929 she stated that for 4 years there was a "black spot" about the size of a pinhead situated in the left scapular region. She observed that this had become irritated as a result of continued rubbing of the shoulder straps and had grown noticeably. A physician removed the growth

with an electric needle June, 1928. Three weeks later the growth reappeared and grew more rapidly.

In May, 1929, our examination revealed on the left scapula a brownish, pigeon-egg-sized, papillomatous growth which bled easily. By means of the electrocautery knife we excised an area of skin, subcutaneous tissue, and fat 6 inches in diameter, leaving muscle tissue exposed. An application of radium was then applied to the affected area.

One month later an enlarged cervical node on the left side was removed for biopsy. The pathologic examination by Dr. Nicholas M. Alter revealed "metastatic melanocarcinoma of the lymph node." Two Roentgen ray treatments (filtered) were applied to the cervical nodes.

On July 19, 1929, Dr. R. Franklin Carter performed a plastic operation. He reported: "At the time of operation, examination revealed a large ulcerated area over the supraspinal space of left scapula, approximately 2 or 3 inches in size with numerous hard nodes in the inferior deep cervical region, nodes freely movable. Just below the angle of the mouth, left side, there was a dark papillomatous growth."

FIG. 8.—Postoperative, January 6, 1934, site of cheek lesion.

Operation. "Area of ulcer on back excised by triangular incision with base toward the arm, 6 by 7 inches. All tissue excised down to muscle. This space was filled by sliding an equal area from below the dress line into the area of excision. The lower space was covered with a Thiersch graft."

Second Operation. "Five days later, block dissection of the nose and left side of omohyoid group and all inferior deep cervicals and excision of tumor from left cheek which had been recently growing larger and becoming darker."

Following the operation the patient's wounds healed readily, except the spaces between the Thiersch graft. Pinch grafts were used to fill in these areas all of which finally healed. Keloid formation grew rapidly in all the scars and was subsequently treated by Roentgen rays. There was no post-operative Roentgen therapy directed toward possible metastasis.

Dr. Alter's pathologic report of tissue removed from the back by Dr. Carter revealed "benign chronic ulcer." The nodes of the neck on section presented melanocarcinoma. The mole from the left cheek proved to be "melanocarcinoma."

Following the operation Dr. Carter noticed a rapid enlargement of many brown moles of the usual congenital type. These assumed characteristics which were suspicious of malignant change. However, as the patient's wound healed, there was a noticeable regression of the moles. They resumed a quiescent appearance, becoming smaller and flattening out.

The patient was examined by me on January 6, 1934, at which time there was no evidence of metastasis. The wound had healed entirely and there was no evidence of a recurrence. The other moles present have retained their innocent appearance.

Summary. The interesting features in this case are:

1. Rapidly growing melanocarcinoma with metastasis to adjacent glands demonstrated microscopically.
2. Peculiar flare-up after removal of tumor and lymph nodes of pigmented moles on various parts of body with recession without treatment.
3. Appearance of melanocarcinoma on left cheek which was removed surgically without recurrence.
4. Patient has gained weight and has had no recurrence in $4\frac{1}{2}$ years.

MULTIGLANDULAR SYNDROMES RESEMBLING SIMMONDS' DISEASE, WITH CASE REPORT.

By Albert Weinstein, M.D.,
RESIDENT PHYSICIAN, VANDERBILT UNIVERSITY HOSPITAL, NASHVILLE, TENN.

(From the Department of Medicine, Vanderbilt University School of Medicine.)

The clinical syndrome of pituitary cachexia defined by Simmonds,[1] in 1914, has been described infrequently since that time. A recent review by Calder,[2] in which he abstracts the detailed report of 37 cases by Gaubner,[3] in 1924, and reviews the cases published since 1924, would indicate that a total of 70 cases are on record. However, in 1933, in a more critical review, Silver could find but 41 cases which he judged on the basis of autopsy data to be examples of the syndrome. It is noteworthy that only 7 cases (Nos. 4, 5, 6, 7, 8, 9, 10) are reported in the English literature and, of these, only 3 (Nos. 5, 7, 8) were proved by autopsy data. Accordingly, it seems desirable to place on record examples of this clinical picture, particularly when postmortem findings are available.

Clinically the syndrome is seen in women in about 70% of the reported cases. It is characterized by weakness, marked loss of weight, loss of hair and teeth, trophic changes in the skin, gastrointestinal atony, achlorhydria, low blood pressure, lowered body temperature, low pulse rate and a markedly lowered basal metabolic rate. In both sexes there are striking disturbances in sexual

function, with loss of libido and potentia, with failure of spermatogenesis in the male, and amenorrhea in the female. There is usually a moderate secondary anemia and a well-marked eosinophilia. The patients are apathetic and easily exhausted. Mental disturbances are common and may dominate the clinical picture. Hypoglycemia is the rule. The disease runs a progressive course ordinarily, but may be remittent, and authentic cases, untreated, have lived as long as 44 years following the development of symptoms.

Pathologically there is a destruction of the anterior lobe of the hypophysis with secondary atrophic changes in the thyroid, suprarenal cortex and gonads, and with a decrease in the size of the thoracic and abdominal viscera. There may be a simple fibrosis of the anterior lobe with almost complete loss of cellular substance or the destruction may be secondary to tumors, cysts, syphilis, tuberculosis or trauma.

FIG. 1.—Patient in 1928.

Case Report. (Unit No. 55925.) The patient was a farmer (white), aged 27, native and resident of Tennessee. He had always enjoyed excellent health until 1930, when he contracted an ulceroglandular type of tularemia. He remained in bed for a month because of weakness, but soon afterward recovered his normal vigor. In 1932, he developed an infection of the right hand which was associated with fever and weakness. After a period of 1 month, the lesion was incised and healed within a short time. He felt, however, that he never regained his strength. His wife stated that he began to show personality changes at that time.

In January, 1933, he had an illness interpreted as being influenza. He then began to fail, losing weight and feeling quite worn, and noted dull frontal headaches. There were periods of fever, nausea and vomiting. He soon became bedridden. He noted that he felt cold even during warm

weather. The hair of the pubis and axillæ became thin, and he was able to go for longer periods of time without shaving. Libido and potentia were lost.

He had been married for 4 years. His wife was living and well and there had been no pregnancies, although contraceptive measures were not employed. His forebears had usually been in good health.

The patient was admitted to the medical wards on May 24, 1933, for a period of 17 days. Little improvement followed and accordingly he returned on June 29 and remained until the time of his death, on October

FIG. 2.—August 10, 1933.

FIG. 3.—September 20, 1933.

10, 1933. The observations obtained during the 2 admissions may be summarized as follows: emaciation was conspicuous; in January, 1933, he weighed 137 pounds (62.3 kg.), his average weight; at the time of his admission in May, 107 pounds (48.7 kg.); on June 29, 102 pounds (46.4 kg.); and at the time of his death, in October, 71 pounds (32.3 kg.), representing a total loss of 49% of the body weight. He eventually became so weak that he had to be aided in turning in bed (Figs. 1 to 4). The pulse rate was usually slow, 40 to 60 per minute, and the body temperature was also lowered—97° to 98° F. by rectum. There were frequent bouts of fever,

100° to 101° F., associated with an elevation of the pulse rate to 80 to 100. The skin was sallow, thick, wrinkled and inelastic. There was complete loss of axillary hair, marked thinning of the crines and beard, and the hair of the scalp was dry and coarse. There had been a loosening of the teeth, even the non-carious ones, but there was marked Vincent's infection of the gums. There was no general or local enlargement of lymph glands. The thyroid could not be felt. The lungs were clear to physical and roentgenologic examination. Examination of the heart revealed an extremely small organ; there were no auscultatory abnormalities, and the electrocardiograms were normal. The abdominal contents seemed normal in size and this impression was confirmed by Roentgen ray examination of the gastro-intestinal tract. The testicles were atrophic and the prostate was very small. No spermatozoa were noted in the prostatic secretion.

FIG. 4.—October 4, 1933, 6 days before death.

The neurologic examination revealed no striking abnormalities. The visual fields were normal save for a general constriction of the right field found at a single unsatisfactory examination which could not be checked, due to the patient's poor condition. He had frequent attacks of mental upsets, characterized by disorientation, delusions and hallucinations. The blood pressure was 90 systolic and 60 diastolic.

Laboratory examinations showed a moderate secondary anemia, red blood count of 3,500,000 and hemoglobin 10 gm. The total white blood count was normal, but there was a definite eosinophilia which varied between 5% and 40%. Supravital and cell volume studies did not show further abnormalities. Repeated examinations of the stools revealed no parasites, and a biopsy of a lumbar muscle showed no trichina. The urine volume was not abnormal, and the specific gravity varied between 1.003 and 1.012. There were no abnormal constituents of the sediment,

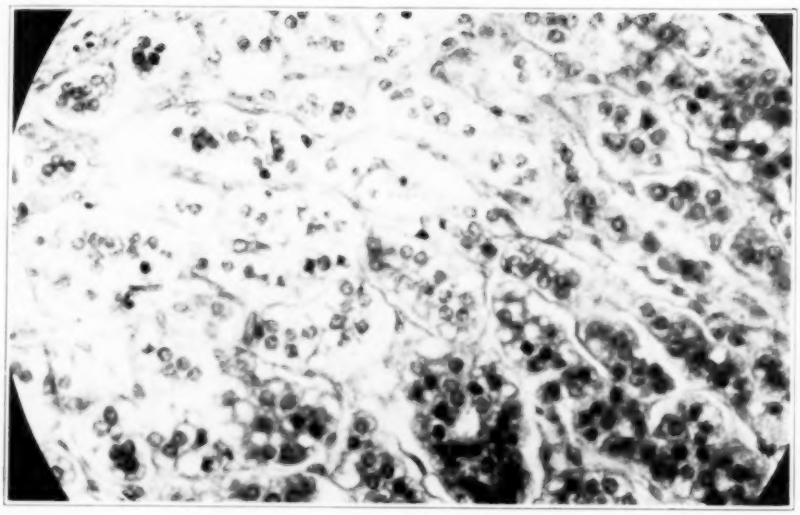

FIG. 5.—Adrenal cortex, showing vacuolization of the cells. H. and E. × 450.

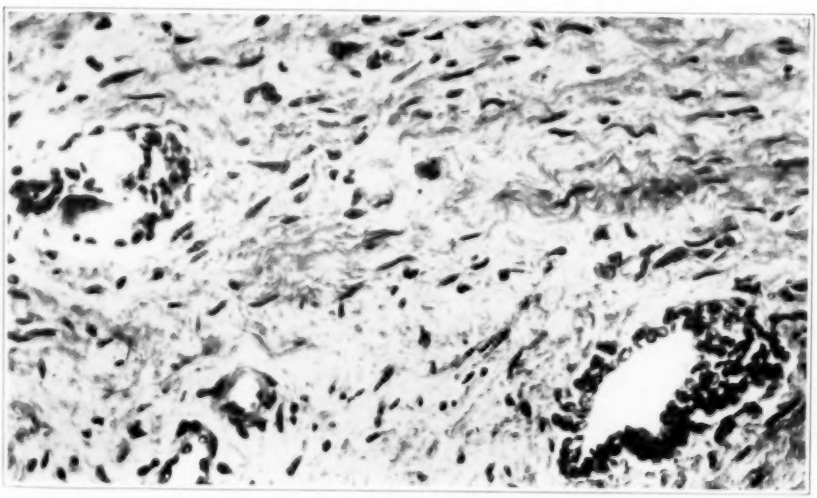

FIG. 6.—Prostate, showing the small acini and the flattened epithelium. H. and E. × 450.

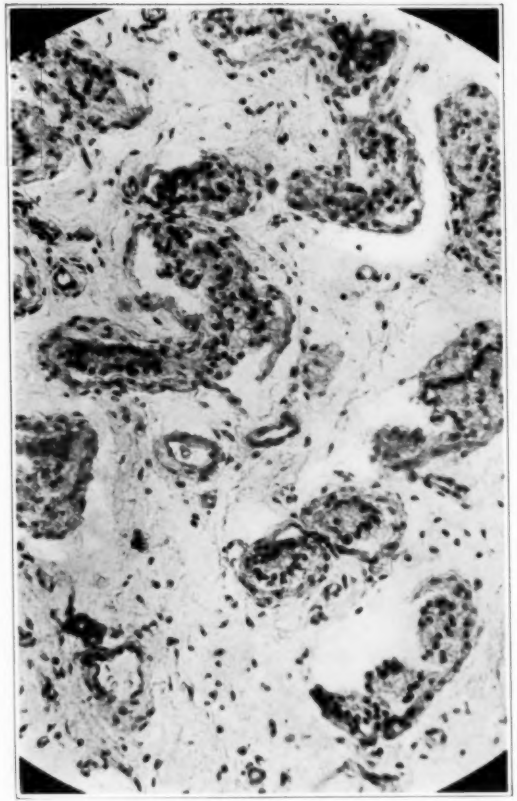

FIG. 7.—Testis, showing marked atrophy of the interstitial cells. H. and E. × 225.

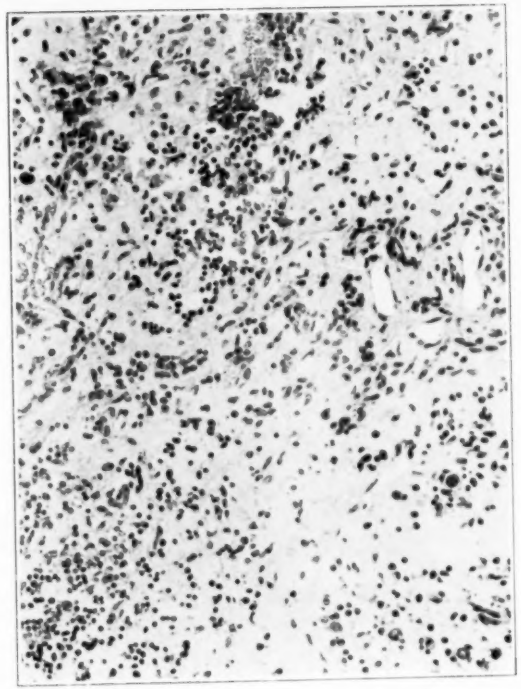

FIG. 8.—Portion of anterior pituitary showing replacement of cellular elements by fibrous tissue and invasion of the gland by neoplastic cells. H. and E. × 225.

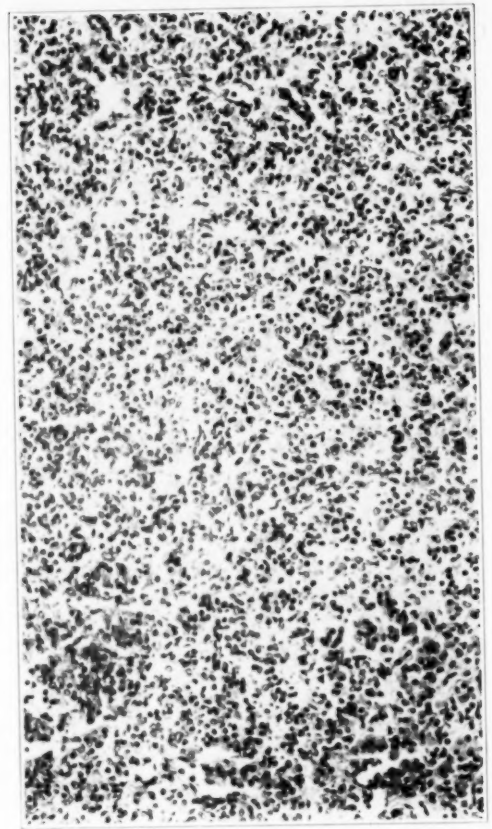

FIG. 9.—Normal area of the anterior pituitary. H. and E. × 225.

and the tests for sugar and albumin were negative. Kidney function tests were normal, blood non-protein nitrogen was 25 mg. % and the phenolsulphonephthalein excretion was 55% in 2 hours. There was a fasting achlorhydria, but following the injection of histamin (0.5 mg.) there was a free acid content of 25 and a total of 36 cc. of $\frac{N}{10}$ sodium hydroxid. Roentgen ray examination revealed a normal stomach and intestinal tract. Basal metabolism studies gave readings which varied between 35% and 42% below normal. The respiratory quotient was 0.67. It is important to note that the basal metabolic rate was −34% before undernutrition became prominent. The fasting blood sugar was always low, 55 to 65 mg. %, and there was increased tolerance to ingested glucose. The blood calcium of 11.6 mg. % and the phosphorus of 3.6 mg. % were normal. Total serum protein was 6.24 gm. per 100 cc., with a normal albumin-globulin ratio. Blood cultures were sterile repeatedly. Agglutinins were present against B. tularense in dilutions of 1 to 640, but all other agglutinations were negative. The Wassermann reactions on the blood and spinal fluid were negative. He was not allergic to intracutaneous injections of old tuberculin. The stereoscopic plates of the skull showed an enlarged sella turcica with thinning of the posterior clinoid processes and with evidence of pressure on the floor of the sella. These signs were interpreted as indicating the presence of a pituitary tumor.

The clinical impression was that the patient had anterior pituitary cachexia (Simmonds' disease).

An attempt was made to better the nutrition by injections of insulin, but he reacted so markedly, with the usual signs of hypoglycemia, even to small doses that they had to be discontinued. When given small amounts of thyroid extract, 90 mg. daily, the basal metabolic rate rose to +4%. At this level he was so uncomfortable that this medication was stopped; as the basal rate dropped he became comfortable again. He was also given 10 gm. of sodium chlorid a day because of possible suprarenal insufficiency. Specific substitution therapy was attempted. Saline suspensions of fresh hog pituitary, 1 mg. of which would cause ovulation in the rabbit, were prepared daily by Dr. Wolfe, of the Department of Anatomy. The patient was given 200 to 400 mg. of the material subcutaneously, daily for a week, with no recognizable effect. He was then given, subcutaneously, 10 cc. of follutein, a sex-stimulating hormone, furnished by E. R. Squibb & Sons, but no response followed, and he died 8 days after these injections were begun.

The report of the postmortem examination, performed 20 minutes after death by Dr. J. R. Dawson, Jr., is as follows:

The body is that of an extremely emaciated white male. It is still warm, and there is no lividity of the dependent parts. The skin is dry, loose and inelastic. The hair is coarse and dry; there is hardly any beard; the pubic hair is scanty; the axillary hair is absent. The penis is of normal size. There is an almost complete absence of subcutaneous fat.

All of the serous surfaces are everywhere smooth, free, pale and glistening. There is no free fluid in the abdomen, and the viscera are normally disposed. They are decreased in size to a moderate degree.

The heart is very small and weighs only 175 gm. The myocardium is dark brown in color and extremely flabby. The left ventricular myocardium measures 1.2 mm. and the right 0.3 mm. The pericardium, endocardium and valves are all normal.

The right lung weighs 300 gm. and the left 220 gm. No gross abnormalities are noted, other than areas of induration.

The gastro-intestinal tract is normal save for moderate congestion and diffuse melanosis.

The liver weighs 1070 gm. The parenchyma is brown; there is no necrosis. The gall bladder and bile ducts are normal.

Fig. 7.—Testis, showing marked atrophy of the interstitial cells. H. and E. × 225.

The spleen weighs 100 gm. The Malpighian follicles are indistinct.

The pancreas is small and weighs 65 gm. The lobules seem to be normal.

The adrenals weigh 4 gm. each. They are obviously decreased in size in all dimensions. On section the cortex is scarcely 1 mm. thick, is extremely yellow and moderately opaque. The medulla is also increased in amount. No fibrosis is noted.

The right kidney weighs 127 gm. and the left 145 gm. There is moderate congestion present. The pelvic, ureteral and bladder mucosæ are edematous, dull, congested and thick.

The prostate is uniformly reduced in size. This is due chiefly to a decrease in the epithelial component without appreciable fibrosis.

Each testis weighs 10.5 gm. The tunic is not thickened. The tubules do not string out.

There is no isthmus to the thyroid gland. Total weight of the 2 lateral lobes is 20 gm. The tissue is firm and brown, and on section little colloid is present.

The parathyroids cannot be located.

The brain seems to be covered with normal dura, and the sinuses are normal. Focal grayish areas of thickening are seen in the pia arachnoid on the convexity of the brain and over the base. No superficial hemorrhages are noted. On section the lateral and third ventricles are seen to be moderately, but definitely, dilated. The foramina of Monro are similarly involved. The ependyma appears granular. The fourth ventricle is normal.

The pituitary gland lies in its normal position. It weighs 0.432 gm. Its capsule is definitely thickened. No division between the lobes is apparent. No degenerative lesions or tumefaction is noted. Fibrosis is not apparent grossly.

Microscopic notes: There is a bronchopneumonia present. The myocardial fibers are smaller than normal, and the liver and spleen are not remarkable.

No lesions are seen in the pancreas. There is no decrease in size of the islands of Langerhans. The acini in some instances are smaller than normal.

The cortical cells of the adrenals are vacuolated. Within these vacuoles are fine reddish granules. No other lesions are noted (Fig. 5).

The acini of the prostate are unbelievably small. The epithelium is very flat, and there is little secretion. There is no increase in fibrous tissue (Fig. 6).

Testes show complete atrophy of all interstitial cells without fibrosis (Fig. 7).

The thyroid alveoli are moderately decreased in size and are lined by very flat epithelium, but the colloid is normal in amount and appearance. No evidence of inflammatory reaction is seen. Parathyroid tissue was not seen in the blocks of tissue studied.

Examination of the brain by Dr. E. W. Goodpasture:

"Involving the region of the base of the third ventricle and extending into the hypophysis is an invasive, superficial, diffuse tumorous growth of large oval round or polygonal cells with vesicular nuclei and abundant well-defined cytoplasm, often discrete, not infrequently in loose groups which are intimately related in their growth with the ependyma, beneath and in which it is chiefly recognizable, infiltrating superficially into the surrounding brain tissue. There is much inflammatory almost granulomatous reaction associated with the growth. Mitotic figures are not numerous, but present. Large tumor giant cells are not infrequently seen.

"The growth extends, perhaps continuously, although grossly imperceptible, from the third ventricle beneath and in the ependyma back to the

floor of the fourth ventricle in the medulla. In places, especially the last-mentioned, the cells have the appearance of neuroglia with a few of the discrete cells intermingled.

"It is this tumorous growth which involves the hypophysis and partly destroys it. It is responsible also for the moderate internal hydrocephalus, probably narrowing the Aqueduct of Sylvius.

"As to its nature I am not at all certain, but owing to its intimate relation with the ependyma, its spread beneath it to distant parts, and the apparent transitions in form between epithelial-like, discrete cells to coarse neuroglial cells, I am inclined to a diagnosis of an Ependymal Glioma" (Fig. 8).

The pituitary gland was studied by Dr. J. Wolfe. After fixation in Regaud's fluid for 24 hours the gland was halved in a sagittal plane and then fixed for a further period of 4 days, after which it was postchromated for 8 days, washed in running water for 24 hours, dehydrated and embedded in paraffin. Both portions were cut in serial section in the horizontal plane. The right half of the gland was entirely destroyed, including posterior, intermediate and anterior lobe. The globular cells were replaced by a coarse connective tissue. The left portion of the gland was essentially normal. Cell counts were made on 11 sections at definite intervals apart. The eosinophils averaged 32%, the basophils 7% and the chromophobes 61%. All cells were normal.

Considering the gland as a whole, approximately 35% of the anterior lobe material was morphologically normal (Fig. 9).

Pathologists' conclusions: There is atrophy of the testes, prostate, seminal vesicles and thyroid without extensive fibrosis. The pituitary is invaded by a tumorous growth, probably an ependymal glioma. The prostate and seminal vesicles are of the type seen in the castrate. The viscera, in general, are reduced in size far beyond that which would be predicted for the degree of emaciation.

Discussion. It is important to point out that the clinical picture presented by this patient was compatible in every respect with the syndrome outlined by Simmonds, even though 30% to 35% of the anterior hypophysis remained. From the experimental observations of Smith,[11] we find that only 10% to 15% of the anterior pituitary gland is necessary for normal metabolism in the rat. However, we do not know what fraction of the anterior hypophysis is necessary for normal body function in the human being. In addition, one cannot say from histologic studies that glandular tissue is functioning normally.

The relationship between the observed changes in the pituitary and the repeated infections that the patient had cannot be evaluated. They may have conceivably played the part that the puerperal infection did in the original report by Simmonds, although we had no evidence that infected emboli were present.

The favorable results previously reported, particularly those by Brougher[10] and Calder,[9] are open to criticism. The case reported by Brougher had evidence of an adjacent tumor and the pituitary involvement was plainly secondary in importance. The patient studied by Calder was markedly emaciated when injections of antuitrin were begun, and he started to improve soon afterward. However, he continued to improve during the five months of

observation included in that report, even after the injections of the extract had been discontinued. If the residual pituitary function was so slight that it resulted in the clinical picture of profound emaciation, it is odd that the improvement should continue even after the substitution therapy was stopped. It is logical to believe that, in the future, substitution therapy will become practical in the treatment of this condition, particularly when the diagnosis is made before irreversible changes take place throughout the endocrine system. It is equally likely that, similar to other forms of substitution therapy, it must be continued indefinitely. The evaluation of glandular therapy is to be made with the greatest care, particucularly since we are dealing with a disease which, as indicated above, undergoes periods of spontaneous remission and since patients untreated live as long as 44 years following the development of signs and symptoms of this condition.

That this patient had a pluriglandular syndrome is definite. As emphasized by Kraus,[12] it is usually impossible to attempt to differentiate these conditions pathologically unless the hypophysis is involved, as in this instance, by a process different from that affecting the other glands of internal secretion. In some there seems to be a primary atrophy of the pituitary with secondary changes in the structure of the other endocrine glands and disturbances of function, as described by Simmonds; in the syndrome of Lindemann there is a general atrophy of all the glands, occurring simultaneously; and in others, a sclerosis occurs in all the endocrine glands (Falta). Since the clinical manifestations of these varied conditions may be very similar, the correct prediction of the character of the pathologic changes underlying these syndromes may become a matter of chance.

Summary. This patient, then, presented the characteristic evidences of Simmonds' disease, yet at autopsy there remained 30% to 35% of histologically normal anterior hypophyseal tissue. In the strictest pathologic interpretation of this syndrome the patient did not present one of the features of the disease, that is, complete destruction of the anterior pituitary, but the clinical picture was so nearly identical with the previous reports that it seemed desirable, particularly in view of the careful clinical and histologic study to which this patient was subjected, to place this case on record.

Conclusion. 1. The history, physical findings, progress and autopsy data of a patient with Simmonds' syndrome are presented.

2. The pituitary was invaded by an ependymal glioma and atrophic changes were present in the thyroid, suprarenal cortex, testes and prostate.

3. Certain aspects of treatment of the condition are discussed.

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ON THE ENDOGENOUS ORIGIN OF EARLY PULMONARY TUBERCULOSIS. THE ANATOMIC VIEW OF ITS CLINICAL DIAGNOSIS.

By W. Pagel, M.D.,
CAMBRIDGE, ENGLAND.

(From the Laboratory of the Papworth Village Settlement.)

In order to make an early diagnosis of tuberculosis it is necessary to be able to recognize the foci which introduce the common pulmonary lesion. It is also necessary to know the channels used by the tubercle bacillus, and the usual location of the foci which they produce.

The common pulmonary tuberculosis of the adult which is the subject of an early diagnosis is not the first manifestation of tuberculosis in the life of the individual concerned. The primary tuberculosis occurs during youth and heals, leaving a group of calcified lesions which are quite characteristic. Furthermore, the common pulmonary tuberculosis is not a form which follows the primary infection immediately (or after a short interval), like the generalization which in its acute form is an immediate offspring of the primary infection.

The form of tuberculosis which is the subject of our discussion develops after the primary infection has healed, without generalization. We know that the primary infection comes from outside, originating in an inhalation of droplets or dust of sputum containing bacilli into the lung; or in ingestion; or in direct inoculation into the skin, etc. It is obvious that generalization of tuberculosis develops by series of hematogenous outspreads, since it leads to a tuberculosis of bones, joints, urogenital system, meningitis, to chronic miliary outspreads in the lung, "punched cavities," etc. (Pagel, Miller). But the common tuberculosis of the adult is a

tuberculosis involving the lungs only, and proceeding by the way of the bronchi and the great channels being in connection with them like trachea, larynx, intestine. Thus it might be assumed with equal right that an exogenous or endogenous reinfection is the origin of this common form of tuberculosis, and as a matter of fact the opinion as to the origin of the isolated pulmonary tuberculosis is divided. (See Discussion, Cummins, Cobbett, Aschoff, Pagel.) One group of authors stresses an exogenous superinfection as its source (Puhl, Beitzke), another suggests an endogenous and hematogenous metastasis from old primary or postprimary foci to be the origin of the isolated pulmonary tuberculosis (Ghon, Schmincke, Wurm, Huebschmann, etc.).

It is not possible to approach successfully the question of the exogenous reinfection by anatomic investigation. There are clinical and epidemiologic data suggesting the possibility of exogenous superinfections for the development of the isolated pulmonary tuberculosis. In early cases one has found a current source of infection in the environs of the patient (Assmann, Ulrici). Further, it has been demonstrated by animal experiments that superinfection of a tuberculous—allergic—animal can produce an isolated tuberculosis of the lungs, if the primary infection was mild, *e. g.*, due to an avirulent or faintly virulent strain of tubercle bacilli (human strains in rabbits, Pagel, Cobbett; B.C.G., Aksjanzew and Krewer; leprosy bacilli, Bieling and Oelrichs).

But anatomic experience points to the endogenous reinfection as a great possibility for the development of an isolated pulmonary tuberculosis. This endogenous reinfection originates in a revival of old lesions, due to factors which diminish the resistance, such as diabetes, pregnancy, puerperium, old age, etc.

There are findings of exacerbation of the foci of an old primary complex, at the site of the primary focus of the lung as well as in the lymphatic glands. I have observed such phenomena of exacerbation in about 25% of my cases. They are much more frequent in the *glandular part* of the primary *complex* than in the *primary focus* of the *lung itself*.

Here we find the calcified foci embedded in areas of recent caseation. Such cases occur especially during *puberty* and *older* age; *e. g.*, I found in a woman, aged 88, who died from nephrosclerosis, that the *lymphatic glands* of the bifurcation of the trachea were tumefied and caseous and were the only tuberculous foci (besides a small calcified primary lesion in the upper right lobe of the lung). The recent caseous tuberculosis had developed in the environment of the old calcified primary focus in the lymphatic gland of the hilum.

The following is an example of caseous exacerbation of the old calcified primary food in the lymphatic glands during puberty. Girl, aged 15, in the beginning of the menstruation. Caseation of

the lymphatic glands of the lung hilum to a great extent, proceeding upward to the jugulum and downward *via* the posterior mediastinal lymphatic glands to the periportal glands and to the mesentery. Typical calcified primary focus in the left upper lobe. In each

FIG. 1.—Calcified foci in the lymphatic nodes of the hilum belonging to the primary complex, surrounded by areas of recent caseation (exacerbation of the old primary foci). ←, Advanced pulmonary tuberculosis.

lymphatic gland every calcified focus is surrounded by a circular area of recent caseation (caseous exacerbation) (Fig. 1). The intensity of caseation decreases according to the distance from the lymphatic glands belonging to the pr mary focus.

FIG. 2.—Calcified focus (*c*). Recent addition to the internal layers of the fibrotic capsule (*e*) with formation of epithelioid cells. One giant cell (*g*). Low power.

A recent caseation around the primary focus in the lung itself is found less frequently. We have recently seen an example of the lung of a man, aged 30, with a large cavity in the left upper lobe and advanced intestinal tuberculosis. In the left lower lobe

there was an area immediately beneath the pleura containing the old calcified primary focus of the size of a lentil as the center of a recent caseous focus of the size of a small cherry (caseous exacerbation of an old primary focus in the lung).

The histologic examination of such foci in exacerbation demonstrates sharply confined areas of epithelioid cells recently developed, which interrupt the fibrotic capsule of a calcified focus (Figs. 2 and 3). Probably the fibrotic connective tissue of the capsule has returned to its original cellular state under the influence of the exacerbation, as described by Wurm. Or we find areas of tuberculous granulations, containing epithelioid and giant cells, invading the marginal parts of the focus and restoring the calcified caseous material (Fig. 3).

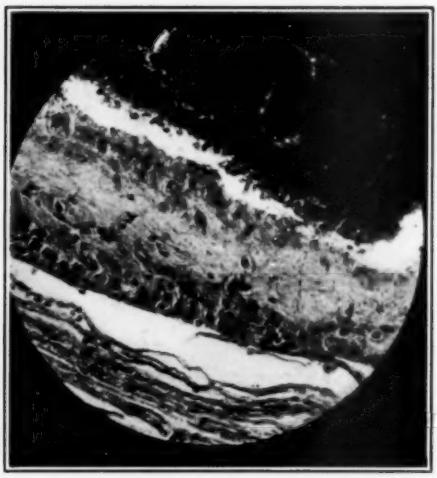

FIG. 3.—A calcified focus in the state of exacerbation. The calcified center (*C*) surrounded by a thick fibrotic capsule (*F*), the external part of which returned to the original cellular stage by recent exacerbation (*E*). The external margin of the focus consists of fibrotic connective tissue again. Higher power.

We know that about 20% of the old calcified foci of the primary complex contain living tubercle bacilli (Anders). There are also lymphatic connections of the old foci with the surrounding tissue.

So the foci of an old *primary* complex can be permanent sources for an outspread of tubercle bacilli into the blood stream.

Clear is the proof that outspreads arise from exacerbating post-primary foci.

We know that isolated regular calcified foci in the apex of the lung can be rich in living bacilli. The tubercle bacilli in such foci can be detected, after artificial removal of the calcium, as complete colonies.

After staining with Giemsa's solution I found the bacilli in such calcified foci "eosinophilic," while the bacilli are usually "basophilic." According to the behavior of the bacilli in cultures, this eosinophilic state points to an inactive state of the bacilli in calcified foci.

The calcified foci that are the subject of our discussion are due to a hematogenous outspread, because of their frequent presence in cases of chronic hematogenous generalization, during which they remain usually inactive, while they proceed by liquefaction and consequent aspiration in cases of beginning isolated pulmonary tuberculosis. There are all transitions between miliary outspreads of calcified lesions which point to their hematogenous origin and the occurrence of isolated calcified foci in the lung.

These foci may be found in the center of a larger caseous focus and there is no doubt that their exacerbation leads to the development of the larger focus which does not become the origin of a proceeding isolated tuberculosis of the lung.

E. G., a male, aged 60, showed in the apex of the right lung a large liquefying caseous infiltration of the size of a halfcrown. In the middle of the infiltration there were 3 small calcified foci of the size of a small lentil. The histologic examination showed all signs of exacerbation, such as interruption of the capsule, beginning liquefaction, etc.

The calcified foci are scattered over the lung or are confined to particular areas, especially the apex. One of our cases demonstrated a calcified focus in the "azygos" part of the left upper lobe, causing the formation of two apices of the lung. Woman, aged 26, isolated advanced pulmonary tuberculosis. Left upper lobe with abnormal division (Lob. azygos). One small yellow calcified focus in the left apex, another in the lower parts of the lobe, with a corresponding calcified focus in a bronchopulmonary lymphatic gland ("primary complex").

Another way leading from the calcified focus to the development of an isolated pulmonary tuberculosis is the aspiration of such a focus and its transmission to other parts of the lung by the bronchi.

Old calcified primary or postprimary hematogenous foci cause very often by their shrinking a small bronchiolectasis, from which the early foci of a progressive isolated pulmonary tuberculosis start. There arises then not a hematogenous form, but one which is endogenous and bronchogenic.

After liquefaction and eruption of the exacerbating calcified lesions into the "parafocal" bronchiectases, caseous material rich in tubercle bacilli is aspirated to other parts of the lung, where recent foci develop which now introduce the progressive pulmonary tuberculosis.

E. G., male, aged 36. Mother died from tuberculosis. Chronic tuberculosis the last 10 years. Avulsion of the right phrenic nerve.

Died from insufficiency of the heart. Shrinking of the right upper lobe. This is interspersed by a series of small bronchiectases, the wall of each containing a calcified focus. Similar, but not so many, lesions in the left upper lobe. Recent caseous cavity of the lower part of the left upper lobe with numerous tubercle bacilli.

EARLY (POSTPRIMARY) TUBERCULOUS FOCI OF THE LUNG AS AN INTRODUCTION TO THE COMMON ISOLATED TUBERCULOSIS OF THE ADULT.

	Hematogenous.[1]	*Bronchogenous.*[2]
Apex	1. Discrete miliary and dense fibrous. 2. Small calcified foci. 3. Small bronchiectases with calcified foci in the neighborhood. 4. Larger caseous or calcified foci ("Fruehinfiltrat" of the apex).	1. Independent exogenous superinfection of the apex (?) with caseous bronchitis ("Fruehinfiltrat" of the apex). 2. Aspiration into the apex from a non-apical focus.
Infraclavicular region[3] Foci occurring anywhere in the lung	1. Larger caseous foci without apical lesions, so-called "Fruehinfiltrat" (precocious infiltration). 2. Larger caseous foci developed at the same time with apical, subapical and horizontal location. 3. Hematogenous caseous bronchitis.	1. Independent exogenous caseous foci and caseous bronchitis with or without other independent—apical—foci, developed at the same time from outside (typical "Fruehinfiltrat"). 2. Infraclavicular foci by aspiration from other previously developed foci, especially in apex ("Pseudofruehinfiltrat").[4]

[1] The proof of the hematogenous origin of all these foci is the anatomic evidence given by their presence in cases of chronic hematogenous generalization. During this period they remain usually inactive and calcify, while they proceed by liquefaction and aspiration in cases of isolated pulmonary tuberculosis. The ability of the apical hematogenous foci (1 to 4) to become the source of a progressive pulmonary tuberculosis is obvious from (*a*) their content of bacilli, (*b*) the pictures of cellular activation of the old capsule, (*c*) their "atheromatous" liquefaction, (*d*) the eruption of liquefying calcified lesions in the small bronchiectases described under 3. The apical hematogenous foci demonstrate a definite tendency to heal and to remain inactive.

[2] There is no anatomic evidence of the exogenous development of the foci. In animal experiments exogenous superinfection is possible, when the primary infection of the animals was due to a faintly virulent or avirulent strain of bacilli. Clinical observations of exogenous superinfection are reported.

[3] The foci show a tendency to become the source of daughter foci and the onset of a progressive isolated pulmonary tuberculosis.

[4] There are anatomic observaions of such foci.

In cases of chronic hematogenous tuberculosis we usually find small cavities in the upper parts of the lung embedded in thick strata of connective tissue. They are often hidden in small fibrosed areas and may not be detected by the Roentgen ray picture. We are justified in suggesting a hematogenous origin of these small cavities. In spite of their shrinking and their concealed situation they can be the source of a bronchogenic outspread of tubercle bacilli, producing the development of recent foci in lower parts of the lung. These foci, developed by a bronchogenic outspread from

a small hematogenous cavity, become now the early infiltration introducing the isolated pulmonary tuberculosis.

So we can demonstrate by anatomic investigation in more than one way the importance of an endogenous outspread for the development of the isolated pulmonary tuberculosis.

It is an isolated hematogenous metastasis in the lung from which the process arises; the focus may itself after a period of inactivity become the center of an early infiltration or may only be the source for living virus which is conveyed from this focus to other parts of the lung by the ways of the bronchi on the bloodvessels.

It remains to discuss the usual *place* where the early foci of the isolated tuberculosis of the adult in the lung are found. The improvement of the Roentgen ray technique in the last years brought about a change in the fundamental clinical view of a very recent tuberculosis. While we formerly tried to localize the early stages of a pulmonary tuberculosis in the apex of the lung, we have now learned that the clinical onset of the disease must be looked for in other parts, especially the so-called infraclavicular region (Ulrici; Wessler and Jaches; Assmann, Redeker; Grass; Douglas, Pinner and Wolepor). I stress the clinical onset, because my autopsies show that, as a matter of fact, the first postprimary foci in cases of isolated pulmonary tuberculosis are very often found in the apex. But in spite of this fact the clinical statement is correct. The majority of the apical lesions have a tendency to become quiet and inactive, while the infraclavicular lesions, being larger, can liquefy after a short interval and, as the so-called "early cavities," may become the source of daughter foci developed by aspiration and finally of the intestinal tuberculosis resulting in the death of the patient, unless the foci within the lung have not already proved fatal. But it must be pointed out that foci in the apex are usually present, that these also may be the original source of the intraclavicular "early infiltration" or eventually, if they are large, by their liquefaction the immediate source of a progressive tuberculosis.

Usually we find in the *apical* region, *as well as* in the *infraclavicular* district, early lesions. According to the quality of these foci it seems that they have developed almost at the same time and that they are usually independent of each other.

I give two examples of such forms:

Case 1.—Male, aged 35. Chronic hematogenous tuberculosis (advanced urogenital tuberculosis, caseous tuberculosis of both suprarenals, of the sacroiliac joint, of the second rib, transverse colon, etc.). Died from amyloidosis. Lungs: In both upper lobes in the region of the apical and horizontal branch of the posterior bronchus are well confined caseous partially calcified foci ("early infiltrations"), the apical focus being smaller than the horizontal focus, which was about the size of a halfpenny (Fig. 4). In the apex of the right lower lobe, recent caseous infiltration with the same feature. Miliary outspread in both lower lobes.

The features of the foci suggest that they are due to the same hematogenous outspread. They must have been developed at the same time independent of each other.

Besides this, the presence of a chronic hematogenous generalization and the symmetric outspread of the foci on both sides points to their hematogenous origin.

FIG. 4.—"Early infiltration" ("Assmann's focus") (*a*) in the infraclavicular region (belonging to the horizontal branch of the posterior bronchus of the upper lobe), and (*b*) in the apex.

The *apex* was involved *as well as* the lower ("infraclavicular") districts. If the foci are to be the origin of a progressive pulmonary tuberculosis, the larger foci in the caudal region would probably become the immediate source of aspirations by liquefaction and thus the "early infiltration." Furthermore, it may be that the smaller apical lesions did not appear in the Roentgen ray picture. But the suggestion that the apex is not involved in such a case of early tuberculosis would not be correct.

Actually, the early foci did not proceed and did not cause metastasis by bronchogenic aspiration and thus a tuberculosis of the common type of pulmonary phthisis, because they belonged to a case of hematogenous generalization and not to the common isolated pulmonary tuberculosis. Generalization and isolated pulmonary tuberculosis being the fundamental forms of tuberculosis during the human life exclude each other (Pagel).

But the *type* of the early foci in the apical and infraclavicular areas of the lung is the *same* in cases of generalization and isolated pulmonary tuberculosis. It is only the fate of these identical foci which *differs:* in the case of generalization the tendency is to heal, to calcify and to become inactive; in the case of the common

isolated pulmonary tuberculosis the tendency is to liquefy and to proceed by bronchial aspiration.

Case 2.—Man, aged 30. Tuberculosis of the right upper lobe with cavity. "Azygos" lobe of the left upper lobe. Deformity of the sternum which caused a deep oblong (frontal) impression in the anterior surface of the right ventricle. This was dilated in its right part, including the atrium and the part devoted to the inlet of the venous blood, while the left part of the right ventricle was stenosed.

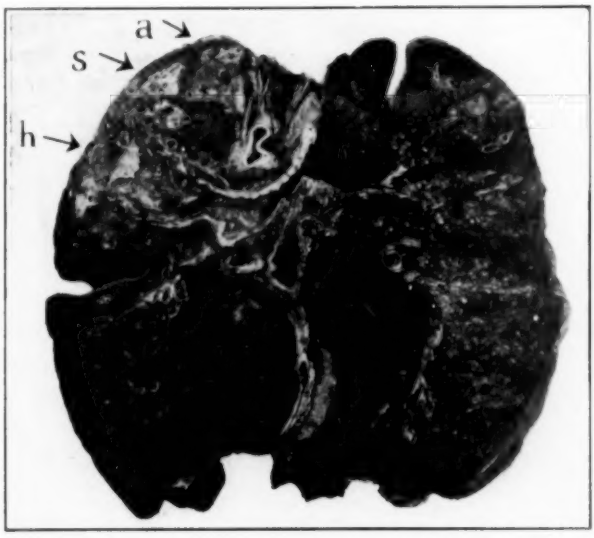

Fig. 5.—Apical (*a*), subapical (*s*), horizontal (*h*) early foci. The horizontal ("infraclavicular" *Assmann's*) focus is the largest and demonstrates an early cavity (liquefied *Assmann's* focus), while the apical and subapical foci are small in spite of their liquefaction. "Azygos," part of the left upper lobe (double apex). Early isolated pulmonary tuberculosis caused by deformation of the right ventricle of the heart.

This contraction of the outlet of the right ventricle may have diminished the blood supply to the lung. To this the tuberculosis of the right upper lobe may be due, just as we find tuberculosis in cases of congenital stenosis of the pulmonary artery. The tuberculosis in this case is not very advanced. The immediate cause of death was insufficiency of the heart with blood stasis to a great extent. That explains why we still find, in the right upper lobe, the foci which have introduced the tuberculosis in this case. There are foci in the three areas of the apical, subapical and horizontal bronchus of the upper lobe (Fig. 5). The horizontal focus only has a remarkable size. It is a cavity of the size of a large walnut. The foci in the apex and the subapical region are also liquefied, but much smaller in size. According to the quality of the foci (capsule,

etc.), it was obvious that all 3 foci developed at the same time, but the horizontal focus became the largest and the liquefaction was more extensive than in the other foci.

In other cases we find that one of these early foci is the metastasis of the other developed usually by aspiration, possibly by hematogenous outspread. Thus the infraclavicular "early" infiltration can be a daughter focus from an older apical lesion which revives and proceeds by bronchial aspiration. An example shows this condition clearly:

CASE 3.—Woman, aged 58. Chronic pulmonary tuberculosis. Roentgen ray picture of the chest showed nothing but a triangular shadow in the infraclavicular area of the left upper lobe. The apical region seemed to

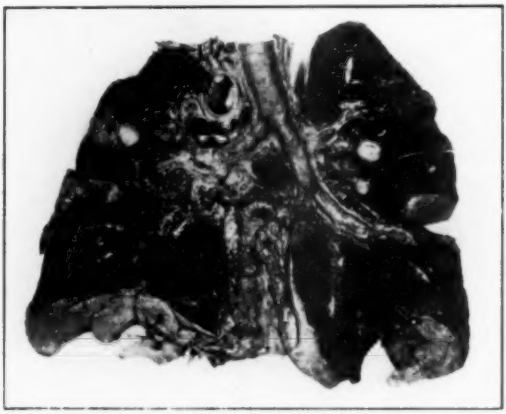

FIG. 6.—"Early infiltrations" in the infraclavicular parts of the lung (due to an aspiration from two very small cavities like burrows made by earthworms in the apex of the posterior part of the lung. (See Fig. 7.)

be normal. The anatomic investigation demonstrated, besides typical "early" caseous infiltrations in the infraclavicular regions (apex of the lower lobe and lower parts of the upper lobe) (Fig. 6), two very small old cavities in the apical and subapical region (Fig. 7). According to the anatomic picture there is no doubt that the more caudal foci, in spite of their typical feature of "early" infiltrations, were due to an aspiration from the older apical lesions.

It should be pointed out that in such cases the Roentgen ray picture does not reveal any changes in the apical region, especially small cavities resembling burrows made by an earthworm (so-called "strand cavities" of Redeker). In other cases I have seen a fibrotic scar of the apex containing small caseous or calcified lesions which did not appear in the Roentgen ray picture while, in the same case, only the larger foci in the subapical and horizontal region were observed.

Thus, in such cases the starting point of the disease, the apical focus, has not been revealed by the Roentgen ray examination and

the clinical impression was that the tuberculosis started from an infraclavicular focus. I am sure that on account of this fact the apical onset of pulmonary tuberculosis is underrated.

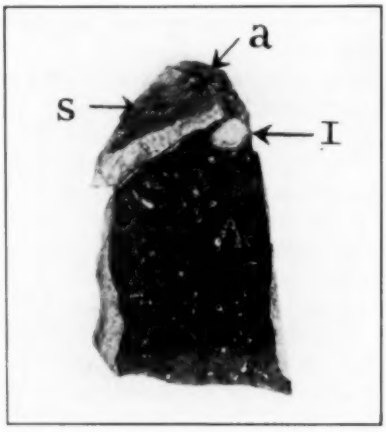

FIG. 7.—"Early infiltration" (*f*) in the apex of the right lower lobe, developed by aspiration from two small "strand cavities" in the apical (*a*) and subapical (*s*) region. Dorsal parts of the lung of the same case as given in Fig. 6.

Left upper lobe. Left lower lobe.

FIG. 8.—Recent early infiltration near the apex (subapical region).

On the other hand, there is no doubt that independent infraclavicular foci are the sources of the tuberculosis—the apex may, or may not, be involved. It is not seldom that the early foci are in a lower position, as in the region of the horizontal bronchus of the upper lobes or near the base.

One of our cases of recent early infiltration showed a big focus near the apex but not exactly in the apical region. Its situation was between the apical and subapical district and it may be that this focus appeared in the Roentgen ray picture as an infraclavicular infiltration (Fig. 8).

Another of our cases was purely an anatomic example of an infraclavicular infiltration.

This case was of a woman, aged 36, with a recent cavity and hemorrhage in the horizontal region of the right upper lobe. Apices contained nothing but small recent nodules.

Conclusion. It may be concluded that all possible ways are used when a common pulmonary tuberculosis arises: the hematogenous and the exogenous or the endogenous-bronchogenous way, etc. But according to anatomic experience, the endogenous course and the revival of previous foci must be regarded as the more frequent. Similarly, foci in all parts occur when a common pulmonary tuberculosis develops. But anatomic experience demonstrates that usually the apex as well as the infraclavicular region are involved, the "infrafocus" may develop as an aspiration of the apical focus or independently. The clinical statement that the "infrafocus" has a greater tendency to become progressive than the apical focus is confirmed by the anatomic investigation. Therefore, the practitioner will very carefully observe the infraclavicular regions, but he should never neglect lesions seen in the apex, especially recent ones. Only experience and careful observation, not doctrine and theory, may help us to avoid mistakes.

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IS THERE A "MORAL CENTER" IN THE BRAIN?*

By N. S. Yawger, M.D.,
NEUROLOGIST, EASTERN STATE PENITENTIARY,
PHILADELPHIA.

While reviewing a book on nervous children my attention was drawn to this surprising statement by Cameron:[1] "The delinquent is made, not born. The term moral imbecile is unmeaning and misleading and should be abandoned . . . . there is no such a thing as a child of high intelligence who, on the point of morals only, is imbecile." Barr[2] says: "Now in *amoral* imbecility there is a partial or absolute absence of moral sense often as complete as in the absence of sight in the blind. This may not necessarily be associated with physical or mental defect, but it constitutes a defect of its own——."

A thumb-nail sketch of a few personalities bearing upon intelligence, emotion and morals may not be amiss. Among the "idiot savants" was "Blind Tom," a colored musician whose talent was very decided. He became famous and gave many concerts throughout America and Europe. He was born a slave and when 7 years old, the family of his master, hearing strange music, found him at the piano. He could at once reproduce the tunes he heard and repeat them after long intervals. Some of his music was from the classics and if it had been played nervously when first heard, that, too, was included in his rendering. "Blind Tom" could play a different tune with each hand at the same time, yet he was so foolish he would arise and, with his audience, applaud his own accomplishments. His intelligence was about that of a child 4 years old.

Jesse Pomeroy of Massachusetts perhaps spent more time—about 40 years—in solitary confinement than has any other prisoner in this country. His crimes began at 13 years and at 14 he was sentenced to life imprisonment and solitary confinement, only having escaped hanging by reason of his extreme youth. Within a few weeks he had stripped, trussed-up, beaten and otherwise tortured a number of little children. Because of these offenses he was detained in a reform school but good behavior procured his release after 17 months. Within the 2 months following, he tortured 2 more children, bruising, stabbing and mutilating them until they died. He made several unsuccessful attempts to escape from prison. While undergoing penal servitude tales were told of his continued cruelty and among other accusations was that of catching rats and skinning them alive. These charges were made by persons outside the prison and were never substantiated by the prison officials. Finally, Pomeroy becoming incensed, brought suit against a lady for $5000 alleging damage to his reputation. He

* Read before the Philadelphia Neurological Society, October 26, 1934.

scored a technical victory—the jury awarded him one dollar. Though repulsive and asocial even as a prisoner, he was intelligent. He read extensively, studied law and acquired some knowledge of several languages.

I have elsewhere referred to the following case:[3] A criminal of high intellectual endowment, robust and a writer of note, began to read at 3½ years and entered upon a life of crime at 9. He became an inmate of two reformatories, three county jails and a penitentiary. He loved the thrill of stealing and the night after his release from a reformatory broke into several houses. Once when arrested there were 29 charges against him including numerous thefts, kidnapping and sodomy. He said he was reared by his grandparents, was always kindly treated as a child, had attended a private school, a primary school and a college. At 21 he inherited $34,000 which he spent in 4 years and later in life received much financial and other assistance from prominent persons; yet he had no feeling of gratitude and for his crimes no self-reproach. He once said to me: "There is a born criminal and I am one." Nor had he much faith in his fraternity, saying: "That there is honor among thieves, is the one good joke accredited to the under-world." With both statements I am in full accord. When last seen he was 48 years old, at liberty—having been granted a pardon through the intercession of many persons—and was then debating whether to return to a life of crime or accept matrimony from a woman of some culture and means. This man is highly intellectual but from his own statements and his crime record, he is an amoral imbecile.

Writing of the Englishman, Griffiths Wainewright, under the caption, "Pen, Pencil and Poison," Oscar Wilde[4] said: "though of an extremely artistic temperament, he followed many masters other than art, being not merely a poet, a painter and art-critic, an antiquarian and writer of prose, but also a forger of no mean or ordinary capabilities and as a subtle and secret poisoner almost without a rival in this or in any age."

At 25 years Wainewright had a long and serious period of depression. He was always exceedingly sensitive to pain, a marked contrast to his moral insensibility where others were concerned. Being a very sensuous man, he would not live without luxuries. It is not known how the strange fascination of poisoning overtook him but in some way he had learned of the lethal effect of strychnin. In dress he was dandified, indulged in perfumes and wore a number of beautiful rings in one of which strychnin was concealed. De Quincey said: "His murders were more than were ever known judicially." Through forgery he acquired control of £5000 which crime was not detected for 12 years. In 1829, having lost their own home through extravagance, Wainewright and his wife were taken into the home of his uncle, Thomas Griffiths. Sometime later the uncle died in convulsions with the married couple inheriting his property. The second victim was his mother-in-law, Mrs. Abercrombe, who with

her two daughters had been permitted to live with him. The reason for her murder is not known but it was thought she may have acquired knowledge of the dangerousness of his character. Later, Helen, a young and beautiful daughter died of symptoms similar to those of her mother. She had been murdered in the hope that the £18,000 insurance could be procured, but the insurance companies became suspicious and refused payment. After a delay of 5 years the case was heard and decided in favor of the insurance companies. Feeling unsafe, Wainewright moved to France where he lived in the home of an old man who was induced to place £3000 insurance on his life. He died some time after and, though Wainewright did not get the money, he felt he had revenged himself on an insurance company. While in France he was detained in jail for some minor offense. Being still wanted in England for forgery, through the arts of a beautiful woman used as a decoy, he was induced to return and was arrested. There were five indictments against him but he was permitted to plead guilty to two and these were not capital in nature. He was convicted and sentenced to transportation for life. While undergoing sentence he would boast of his cleverness as a poisoner and actually made two more attempts to poison persons who had offended him. Havelock Ellis said Lombroso and others would consider Wainewright a "born criminal" or a "congenital criminal" but he preferred the term "instinctive criminal."

Seemingly, as atrocious an intellectual man as ever lived was Gilles de Rais, the original of Bluebeard in the Mother Goose story. Born in a French family of high rank and wealth, this iniquitous monster of the 15th century had all the educational advantages of that time. He could speak three languages and manifested great interest in military matters. At 16 he married, the chief attraction being the wealthy estates of his wife's family. She being a relative of the 4th degree, the Church declared the marriage void, a circumstance that did not for the moment disturb de Rais. Becoming disgusted with his wife, he provided for her maintenance in another part of the castle but upon learning she was pregnant and fearing the embarrassment of an illegitimate heir, he successfully approached the Church, another ceremony was performed and the difficulty thus obviated. Unfortunately, the child proved to be a girl which so angered de Rais that he lost all interest in mother and daughter. In the struggle of Charles VII against England, he rendered distinguished service, fighting beside the Maid of Orleans and later, with others, strove hard to disprove the charges that were paving the way to her cruel death. At 25 he had achieved the high distinction of Marshal of France and retired to this estates. At that period those who dared dispute the doctrines of the Church were punished most severely. Many pleasures were denounced as the work of the devil and their prohibition led to much revolt. It has been believed that these ecclesiastical rigors resulted in the formation of some of the medieval cults giving rise to devil-worship wherein all kinds of

pleasures were indulged and atrocities committed. Books telling of witchcraft, incantations and black magic were read freely. From the undisputed evidence presented at de Rais' subsequent trial, it is believed he may have belonged to one of the most sophisticated, licentious and sadistic of these cults.[5] Be that as it may, there is abundant, well-authenticated historic record of the atrocious orgies in which he and others indulged. At 28, after having been away from his estates for some time, he returned and promptly banished his wife and daughter. Then began the dissipation of his vast fortune wherein he vied with the King in the grandeur of his surroundings. Among others who were invited to join him were two priests, one being his cousin. The assemblage then gathered included artists, actors, poets, musicians, designers, illustrators, astrologers, magicians and others. There was a chapel, a choir and also a laboratory for research in alchemy. The castle was surrounded by a big and ferocious guard while within drinking, carousing and the worst of atrocities were being indulged. Worship of the evil forces called for much human sacrifice. Most of the victims were boys who were trussed-up, cut, slashed and otherwise tortured to death. Such iniquities could not go on forever and the Church finally found him guilty of heresy. The civil authorities then assumed charge, brought him to trial when it was proven that there had been kidnapped or otherwise enticed to his castles 140 children, though the actual number was believed to be much larger. "de Rais was culpable of crimes so horrible that they could be read in open court only if rendered in the Latin tongue."[6] He made full confession, was hanged and the body burned.

Through disease, injury and shock the mind may be strangely affected and this is not recent knowledge, since Oliver Wendell Holmes reminds us that, "A profligate mentioned by Plutarch had a fall and struck his head, after which, he became a virtuous citizen." Lombroso[7] mentions several instances: "Gratry, a mediocre singer, became a great master after a beam had fractured his skull. Mabillin, almost an idiot from childhood, fell down a stair-case at 26 and so badly injured his skull that it had to be trephined; after this he displayed the characteristics of genius. Gall, who narrates this fact, knew a Dane who had been a half idiot, who became intelligent at the age of 13, after having rolled headforemost down a stair-case. Wallenstein was looked upon as a fool until one day he fell out of a window, and henceforeward began to show marked ability."

Some years ago a local surgeon was attempting to increase the cranial capacity of bad boys by means of an incision into the skull; it was his belief that their badness resulted from cramped quarters occupied by the brain. I knew one of his "cures" who was twice afterward in the Eastern State Penitentiary and later an inmate of a jail in New Jersey. *Apropos* of that surgeon's procedure, Dr. Lloyd queried: "Does the good man think he can improve the quality of a nut by boring a hole in its shell?" Another of these

boys had headache, a vicious temper and was a truant. The mother said he had once fallen in front of a railroad train and sustained an injury which she was sure had caused his waywardness. A slight depression was in evidence in front of the skull and this was thought to be the cause of his delinquencies. Two operations were performed and soon after he was an inmate in a reformatory, later a county jail and finally a penitentiary. From the last of these institutions he made a sensational escape by burying himself beneath a cart-load of ashes; shortly after reaching the street he arose, Phoenix-like, and it was not until 6 months later that he was apprehended in California. There is a group of children dubbed the "Apache type" who, in the chronic stage of encephalitis, commit a series of misdemeanors, more or less severe. Recently, Grossman[8] has recorded the case of a very unruly child who became docile after epidemic encephalitis.

Under Constitutional Immorality, Tanzi,[9] discussing the type of individuals that show the permanent insensibility of the ruthless immoral, says: "It is more evident from early childhood, because it is more impressing, notwithstanding the negative nature of its manifestations. In youth, these persons who are immoral through deficiency of sensibility show affection for no one. In their amusements they are placid, silent and cruel. . . . They are not mortified by reproof or humiliated when caught in the act of doing wrong. . . . They neither understand nor value the generous impulses of others; they are skeptical, distrustful and malicious. . . . As there are dogs without the power of scent and flowers without perfume, so also there are individuals devoid of benevolence and sympathy."

There is abundant evidence that the two components of our mentality, intellectual and emotional, need not develop harmoniously. One may be greatly in excess and either may show infantilism. Again, disease or injury of the brain may affect one with little or perhaps no effect upon the other. Hence, "moral imbecile," "amoral imbecile," the "born, congenital, hereditary or instinctive criminal" or "constitutional immorality" are justifiable terms, in the sense that they represent a demonstrable condition, though it is debatable which designation is preferable. Browning,[10] in his analysis of 11 cases of cranial traumata followed by serious moral deterioration but with intellectual integrity, located a "moral center" in the right frontal lobe in right-handed persons. He was convinced that lesions of the first frontal convolution gave rise to irritability, violence and loss of inhibitory power; that lesions of the second and third convolutions gave loss of the "moral sense" leading to absence of shame, fear, sense of duty, and so on. Lehman, quoted by Eng,[11] believes the same brain cells can perform the functions of the intellectual and the emotional processes. Thalbitzer's hypothesis is that there is a particular emotion center and with this Eng[12] is inclined to agree. It is suggested by Piéron,[13] that undifferentiated

emotional reactions may arise at the thalamic level and then be subjected to the discriminating associative intellectual processes at the cortical level.

In regard to a "moral center": Is the cerebral cortex to be regarded as functioning in such a way that local disease or injury could only affect its activity as a whole? Or are there anatomic concentrations, so-called centers, where thought is definitely discriminate, giving such functions as attention, memory, judgment, ideation, special talent, ethical concept, etc.? We have some definite knowledge of motor centers and to a less extent those of sensation, speech and the special senses. However, intellectual and emotional centers are not so easily identified and much more data are needed if we are to be able to establish them.

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THE RECURRENCE OF FACIAL PARALYSIS.*

By Harold R. Merwarth, M.D.,
ATTENDING NEUROLOGIST, BROOKLYN AND METHODIST EPISCOPAL HOSPITALS, BROOKLYN; ASSISTANT CLINICAL PROFESSOR OF NEUROLOGY, NEW YORK UNIVERSITY, BROOKLYN, N. Y.

(From the Medical Service of the Brooklyn Hospital and Department of Neurology, New York University.)

The purpose of presenting the following cases is to call attention once more to the fairly common tendency of the facial nerve to be subject to a recurring paralysis. Of all the nerves the facial nerve

* Read before the Oto-laryngological Section of Kings County Medical Society and Nassau County Medical Society, New York.

is the most susceptible to paralysis: this marked susceptibility as contrasted with other somatic nerves is reflected in the tendency of the paralysis to recur again either on the same or the opposite half of the face. This tendency is not recognized by medical men in general, and often the "neurologist" is not aware of this possibility. It is not mentioned by the authors of modern textbooks dealing with the nervous system.

Oppenheim[1] mentions briefly, "The fact should be noted that facial paralysis, both the rheumatic and the other forms, may relapse; the relapse more often affects the nerve of the other side so that the term is not correct."

A very complete discussion of recurring facial paralysis is given by Bernhard;[2] Huet and Lejonne[3] report a patient with 3 distinct attacks. Langmead[4] reported an instance of a girl with 3 distinct attacks of facial paralysis, always noted in the morning. A very unusual instance of recurring facial paralysis is reported by Mouriquand *et al.*[5] They recite the case of a girl who had 8 distinct attacks within a 2-year period.[5] Orbison[6] reported 2 cases from Dr. Spiller's Clinic.

According to Gowers,[7] "Second attacks of facial paralysis are rare. I have notes on only 5 instances."

The following 19 cases are divided arbitrarily into several groups: The first group consists of those cases which were examined and treated by me in both of their attacks. The first 2 cases were unusual in that they had both halves of the face paralyzed nearly at the same time, a definite period of time separating the onset on both sides.

Bilateral facial paralysis caused by known factors, such as alcohol, arsenic, toxins, syphilis, etc., is not unknown. The occurrence of a bilateral facial palsy of the so-called pure Bell's type, the connotation of which is, "a paralysis of undetermined origin," is fairly rare. According to Gowers,[8] "Fallopian neuritis scarcely ever occurs on both sides simultaneously, although I have more than once known a second attack on the other side to occur within a few months of the first." Harris[9] observes, "Bilateral facial paralysis may occur alone as a double Bell's palsy, though usually there is an interval either of months or years between the affection of the two sides."

Case Reports. CASE 1.—(B.H. No. 18384.) L. C., a large, heavy negro girl, aged 18, was first seen by me, January 18, 1928. At this time, she presented a definite left peripheral facial palsy. It was first observed a few days before by the girl's mother because the girl's face was twisted. As the day wore on the patient became more conscious of her trouble and complained of pain behind the ear and down the neck. While the left face was being observed the right face became completely paralyzed on March 18. She lost the sense of taste completely on both sides and with it her appetite. As a result she lost about 40 pounds in weight up to July 31, 1928. The blood Wassermann test was negative. Spinal

fluid examination revealed perfectly normal findings. Roentgen-ray of skull and mastoids was normal. No focus of infection was observed. The right half of the face recovered completely while the left remained in a somewhat contractured state.

Case 2.—(M.E.H. No. 3252.) Anna Q., aged 11, was first seen, July 19, 1932. On June 24, the left face first became paralyzed. The previous day she had been riding in a car with a breeze blowing in her face. She had also been sitting in a draught in a movie theatre. On July 17, she went in swimming in the ocean. That same evening the right face became completely paralyzed. She had no subjective symptoms. Taste was intact. Tonsillectomy had been performed 2 years previously. General health was excellent. She was observed at regular intervals up to June, 1933. There has been a distinct improvement, although the left face still shows weakness.

Case 3.—(B.H. No. 85560.) Mrs. G. B., housewife, aged 42, was first seen in the dispensary, December 19, 1929, with a paralysis of the right face of 7 days' duration. It was sudden in onset and accompanied by pain in the face; "I was exposed to a draught." In about 7 weeks she had recovered completely. This first attack was attended with considerable anxiety. On October 14, 1930, the patient again returned to the dispensary. At this time the left face was completely paralyzed. Not realizing for the moment that this was a different seizure, I asked her how her face was getting along. She answered, "Why, doctor, this is a brand new spell," and was quite surprised that I did not realize this fact. She was not at all alarmed on the second occasion. The left face felt stiff. She also complained of pains in the left side of the neck. This paralysis recovered in a very short time.

Case 4.—(B.H. No. 44667.) F. H., male, aged 28, on October 25, 1927, developed a right facial palsy. He had no pain, but complained of peculiar feeling in the right face. The right half of the tongue felt numb. Recovery was complete. Three years later, December 9, 1930, he returned with the left half of the face paralyzed. As in the case described above, a similar mistake was made. In scanning the chart hastily, it was thought that this was the same attack previously treated. I was pleasantly surprised to learn that this was a different attack. Two days before the onset of paralysis, the left half of the tongue felt numb and thick. Pain was experienced anterior to the ear around the left border of the jaw. Occasional twitchings of the left face occurred. Objectively the sense of taste was lost on the left. There was no subjective taste disturbance. The face recovered completely by January 20, 1931.

Case 5.—(M.E.H. No. 3513.) S. O., male, aged 32, was first examined, February 9, 1929, because of a right Bell's palsy which had developed on January 22. The right face had improved considerably on March 16. On March 19, the left face became completely paralyzed. He was very much upset. The possibility of a second attack had not been mentioned. He felt that he had been "let down." He suffered much more with this second attack. Pain was complained of behind the ear over the mastoid area. Tinnitus in the left ear and a very annoying persistent taste in the mouth were distressing.

The above 5 cases all had the second attacks of facial paralysis on the opposite half of the face. In all, the blood Wassermann test was normal. Also, urinalysis revealed no abnormal findings. No demonstrable focus of infection could be elicited. No case complained of blisters in the ear or of a watery discharge from the ear.

In the second group are included those patients in whom 1 attack was witnessed by me, who gave a trustworthy history of a preceding attack. It is noteworthy that patients with a second attack are not so apt to be disturbed emotionally by the renewed insult.

Cases with second attack on same side (relapse):

Case 6.—(N.Y.U. No. 580.) M. G., female, aged 25. Left peripheral facial paralysis. Not at all upset by the occurrence. She gave a history of pains "about over the left mastoid process" and had noted a distinct disturbance of taste at the time of onset. Seven years previously, at the age of 18, she had had an attack of facial paralysis on the same side of the face. Her face returned to normal in a comparatively brief period.

Case 7.—(N.Y.U. No. 1703.) W. L., male, aged 50, reported with a right peripheral facial palsy. There was loss of taste, subjective and objective. This patient reported a definite attack on the same side of face 4 years ago. This recovered completely.

Case 8.—(B.H. No. 112681 D.) L. T., female, aged 18, presented a complete right peripheral facial paralysis, with insidious outset. No pain was complained of. She had noticed a disturbance of taste. Loss of taste on this side was proven by testing. According to her mother, and also well remembered by the patient, she had had an attack of peripheral facial palsy on the same side 8 years earlier, which recovered completely. It is of interest that a sister also had a Bell's palsy.

Case 9.—(B.H. No. 11990.) S. O., male, aged 20, reported to the dispensary for treatment of a left facial paralysis. This palsy was noticed a few days ago. The preceding day he had noticed pain behind the left ear and a tendency to watering of the left eye. The weakness was first found out in the morning on arising. He did not complain of any change in taste. Testing showed loss of taste on the left anterior portion of the tongue. Two years before, this patient had had a similar attack on the same side of the face. According to the patient, this paralysis cleared up almost completely.

Case 10.—(B.H. No. 133139.) M. I., male, aged 23, was seen, July 5, 1932. The present attack began a week earlier and was rather insidious in onset. Two days previously he had noticed pain just below the left ear at the angle of the jaw. There was no subjective taste disturbance. He was unable to detect sugar solution on the left half of the tongue. Taste was normal on the right. This patient, on questioning, revealed a previous attack on the same side 6 years before. He recovered completely in a "fairly short" period of time.

Case 11.—(B.H. No. 19603.) E. S., male, aged 35, was seen, in 1926, with a weakness of the right face. He had a mild pain in the right occipital area, but no other subjective complaints or objective findings. He recovered completely. The patient observed that, in 1917, he had had a similar attack on the same side. As far as he could recall, his present symptoms were the same as those of the former attack.

Case 12.—(B.H. No. 72954.) M. Z., male, aged 63, was admitted to clinic with a left facial palsy. This began on April 29, 1929. As occurs in many cases, he went to bed feeling perfectly well and awoke in the morning with the facial palsy. The blood pressure was 152 systolic and 98 diastolic. The patient remarked that 30 years ago, in Glasgow, Scotland, he had had a similar attack on the same side of the face. He soon became well. As a consequence he was not at all disturbed by his present attack.

Case 13.—(Private patient.) J. C., female, aged 21, was seen on June 16, 1929, suffering from a right peripheral facial paralysis, ushered in with pain back of the right ear over the mastoid, arousing a fear of "mastoiditis."

The following day, while working in her office, she found that her mouth did not function properly. She looked into a mirror and found her face was "crooked." She complained of a brassy taste in her mouth. She has had tonsillitis each year for the past 3 years, but recovered completely in 1 month. In 1923, she had a similar attack on the left side of her face, which lasted 2 months, with complete recovery. This attack, in the words of the patient, was worse than the present one.

CASE 14.—(Private patient.) R. F., female, aged 23 (Italian). The third and present attack (right side) began, May 7, 1933, with "a greasy taste" on the right side of mouth. Two days later the right half of face was very painful, including the ear. The patient's first attack occurred in May, 1925, on left half of the face and lasted 1 month. She had a peculiar taste in the left half of the mouth. "I always get a greasy taste in my mouth several days before the attack begins." The second attack on left half of face began in 1930, in the spring. It lasted for 3 weeks. She experienced no pain.

CASE 15.—(B.H. No. 165555.) G. R., male, aged 84, experienced an attack of facial paralysis on the right side 30 years ago, coming on "during the night during a severe thunderstorm." He recovered in 1 week. The second and present attack began 3 weeks ago: "I went to the barber's and had my hair cut. The next few days I noticed a few lumps on the back of my neck and back of my ear. Scabs formed over these (?) lumps. At the same time my right face became paralyzed and it has been paralyzed ever since." Taste was lost completely on the right. He shows a complete right facial (peripheral type), is unable to taste sugar on the right half of the tongue, but does so on the left. There is marked weakness of the orbicularis oculi.

Cases with second attack on opposite sides (associated with diabetes):

CASE 16.—(N.Y.U. No. 693.) P. C., male, aged 56, was seen with a left peripheral facial palsy which recovered in 6 weeks. At this time he was being treated for diabetes: urinary sugar, +; blood pressure, 140/80. He gave a reliable history of a previous attack 12 years before, with a complete recovery. Patient remarks that he has had a successful operation (Talma) for alcoholic cirrhosis of the liver, 10 years ago. He has taken no alcohol since then. The first attack may have been due to alcohol, but the second was a pure Bell type.

CASE 17.—(M.E.H. No. 10998.) A. L., female, aged 60, reported to the clinic, June 14, 1928, with a left peripheral facial weakness. She was receiving treatment for diabetes at the time: urinary sugar, 3.3%; blood sugar, 321 mg. This was her third attack of this nature. In 1925, her right face was paralyzed for a time, and again 2 years ago, in 1926, the the left side was paralyzed, but recovered (same side of face is involved at this time).

Cases of recurrent facial palsy, 1 attack of which was not strictly a so-called Bell's palsy:

CASE 18.—(N.Y.U. No. 1315.) C. O., female, aged 29, reported to the clinic with a definite paralysis of the left face with contracture. Her paralysis was of 3 years' duration. The patient had been suffering from a chronic discharging ear on the left. (This case is not strictly a Bell's palsy, as, in view of the chronic otitis media, it is very probable that the facial nerve was involved as the result of the inflammatory process in the ear.) Twelve years previously she had had an attack of facial paralysis on the right side. She recovered from this seizure completely and showed no evidence of it at her last visit.

CASE 19.—(B.H. No. 65382.) G. W., male, aged 36, following a cold, developed a left facial palsy. This recovered completely in a few weeks. In March, 1928, he had an attack of facial weakness on the right side of his face, associated with tinnitus in his right ear. The facial paralysis cleared up in August, 1928. However, he has been deaf in the right ear since the attack. It is of interest that his blood Wassermann test was 4+. He shows no other evidence of lues of the central nervous system or of more important clinical bearing and presents no other angle or systemic signs or symptoms at this time.

TABLE 1.—SUMMARY OF DATA OF CASES OF RECURRENT FACIAL PARALYSIS.

Case No.	Patient.	Sex.	Age.	Side and times affected.		Interval between attacks.
				R.	L.	
1	L. C.	F	18	1	1	2 mos.
2	A. Q.	F	11	1	1	3 wks.
3	G. B.	F	42	1	1	10 mos.
4	F. H.	M	28	1	1	3 yrs.
5	S. O.	M	32	1	1	6 wks.
6	M. G.	F	25	..	2	7 yrs.
7	W. L.	M	50	2	..	4 yrs.
8	L. T.	F	18	2	..	8 yrs.
9	S. O.	M	20	..	2	2 yrs.
10	M. I.	M	23	..	2	6 yrs.
11	E. S.	M	35	2	..	9 yrs.
12	M. Z.	M	63	..	2	30 yrs.
13	J. C.	F	21	1	1	6 yrs.
14	R. F.	F	23	1	2	8 and 3 yrs.
15	G. R.	M	84	2	..	30 yrs.
16	P. C.	M	56	..	1	12 yrs. (diabetes, Talma operation).
17	A. L.	F	60	1	2	3 and 2 yrs. (diabetic).
18	C. O.	F	29	1	1	12 yrs. (first, Bell's; second, mastoid).
19	G. W.	M	36	1	1	Wassermann, 4+; deafness, N. on R.

Discussion. An analysis of Table 1 causes certain factors to stand out:

Age is no bar to a recurrent facial paralysis. The youngest patient was 11 years, the oldest 84.

The sex incidence was fairly even: 9 females to 10 males.

The intervals between attacks varied between 3 weeks to 30 years.

The possibility of the attack occurring on the opposite side or recurring on the same side is just about even, there being 8 cases with both sides involved and 8 cases with the same side involved. There were 2 patients with 3 distinct attacks in both of which 2 of the 3 attacks recurred on the left side.

Of a total of 293 cases of peripheral facial paralysis treated and examined by the author personally, the paralysis occurred again 19 times (6.4%) from all causes.

The so-called idiopathic, "rheumatic" or "Bell's palsy" occurred again 15 times in 192 cases (7.7%).

Obviously the most common cause of recurrence, as well as the most common cause of paralysis, is Fallopian neuritis or Bell's palsy.

Summary. Nineteen patients with a story of recurring attacks of facial paralysis have been considered. Five of these patients were observed in both of their attacks. The remaining 14 cases gave a reliable history in most cases unsolicited of a previous occurrence.

Just as singly the seventh cranial nerve is the most commonly paralyzed nerve in the body, it is also subject most frequently to recurring attacks.

The frequency is 6.4% from all causes, or 7.7% in cases of a Fallopian neuritis or pure Bell's palsy.

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PATHOLOGIC PHYSIOLOGY OF THE NEUROGLANDULAR SYSTEM.*

By George Crile, M.D.,
Cleveland Clinic, Cleveland, Ohio.

We have been prone to consider that each gland acts independently of all the other glands as well as independently of the nervous system. Not only are there students of individual organs, but there are even students of parts of an organ. Thus there are students of the cortex and students of the medulla of the adrenal glands, of the sympathetic system exclusively and of the brain exclusively. Great progress has been made by these investigators, but many are still apt to think of each gland and of the several parts of the entire nervous system as each endowed with a power of independent initiative and action. It would appear that the time has come when we may put out of our minds the concept that any unit of the great energy system of the organism has inherent initiative.

The organism is normally driven adaptively, that is, only within the range of such activity as is to the advantage of the organism. However, when the various mechanisms of the body, brain, glands, muscles, etc., become so facilitated that they become active beyond

* From paper read before the Philadelphia County Medical Society (Annual J. Chalmers Da Costa Oration), Philadelphia, Pa., April 18, 1934.

the bounds of adaptive and beneficial work, the activity being qualitatively normal but quantitatively abnormal, then we may say that a state of pathologic physiology is established.

When the brain, thyroid and adrenal-sympathetic system are in a state of pathologic physiology, the entire organism is speeded even to destruction and death. When the automatic, self-energizing switchboard and the thyroid and the adrenal glands are equally speeded, hyperthyroidism results; but hyperthyroidism is a misnomer, the term *hyperkineticism* is more exact.

Instead of a pathologic physiology of the entire mechanism, there may be a pathologic physiology of one or of a group of glands, or organs or of the nervous system. The thyroid gland cannot of itself initiate a hyperplasia any more than a motor car can start itself; yet the thyroid gland "comprehends" when it is winter, for it enlarges during the winter. It "comprehends" when the mating season comes, for it enlarges during the mating season; it "comprehends" that some part of the organism has tuberculosis, for it becomes enlarged during tuberculosis. The adrenal glands, likewise, enlarge and become active in winter, in the mating season and in the presence of infection.

When a zebra sees a lion, the brain is the switchboard which throws this switch and closes that switch, passing the impulses to certain muscles, inhibiting others, sending impulses to the thyroid and to the adrenal-sympathetic system, inhibiting the impulses that normally go to the procreative organs, the digestive organs and all that part of the body that will not participate in the action that is about to take place. We have become familiar with the great output of adrenalin and the profound stimulation of the thyroid gland, the sympathetic system and the brain that occurs during the sudden get-away of the zebra. The brain has no power within itself to speed up, but it is speeded up by the adrenal and thyroid hormones. The brain is like a flame glowing all the time and, like any other flame, it flares up under accelerators of oxidation. Thus the sight, smell or sound of one animal may act powerfully on the thyroid-adrenal-sympathetic system of another animal. There is no break in the continuity between the thyroid-adrenal-sympathetic system of the zebra and the thyroid-adrenal-sympathetic system of the lion.

If there is a widespread stimulation of the neuroglandular system, that form of pathologic physiology which we call neurocirculatory asthenia may result. If the excessive stimulation of the sympathetic nervous system involves the pylorus with resultant sphincterismus, that form of pathologic physiology which we call peptic ulcer may be produced; if it involves the intestines, that form of pathologic physiology which we call spastic constipation may result. If the disturbance of the function of the pancreas continues, that form of pathologic physiology which we call diabetes may

result. If the continued activation affects several glands—the pituitary, the thyroid, the adrenals, the pancreas, the gonads, that form of pathologic physiology which we call polyglandular disease results.

These diseases which result from a pathologic physiology of the neuroglandular system are peculiar to civilized man. Hyperthyroidism, neurocirculatory asthenia, peptic ulcer, diabetes, polyglandular disease do not appear in animals in the wild state and rarely in domesticated animals. They are exceedingly rare in primitive man and are uncommon in the lower ranks of civilization. The more highly civilized man becomes, the more prevalent do these diseases become.

We have spoken of the pathologic physiology of the brain-thyroid-adrenal-sympathetic system as the result of *continued* activation or stimulation. Pathologic physiology of this system may likewise be the result of repeated stimulations, that is, there may be a training or education in pathologic physiology. In a man or woman who is predisposed by heredity and temperament to excessive fears, worries and strivings, or who, though normally poised, is excessively driven by misfortune, permanent changes may be wrought. Just as by repeated repetition in school the action patterns of the schoolboy's brain are created and subjected to a specific facilitation by his teacher in his training and education, just as repeated painful injuries facilitate pain, just as agreeable or disagreeable personalities facilitate attraction or repulsion, just as repetition produces habits, discontents and familiarities, so repeated activations in the neuroglandular mechanism cause such excessive facilitation that *normal* stimuli produce *abnormal* reactions. In other words, there may be a process of training and education in pathologic physiology analogous to training and education in Latin and mathematics.

Not only may the nervous system be facilitated or educated to disease as well as to health, but the nerve pathways, ganglia and synaptic junctions also presumably may be facilitated for either good or evil, and under pathologic stimulation the cellular structure of the thyroid gland may grow in actual size and thereby secure for itself an increased capacity for work. That is to say, we may think of chemical training or education by repeated stimulation, no less than of physical training or education by repeated stimulation.

In some such manner an hereditary predisposition played upon by adverse factors in the environment or in a normal individual under excessive strain, in one case may be looked upon as producing hyperthyroidism, in another as pathologically sensitizing the adrenal-sympathetic system, in another as "stepping-up" the brain to its breakdown, or so facilitating the digestive mechanism in its activations and its inhibitions as to cause spastic colitis, hyperacidity, peptic ulcer or indigestion. In some individuals, the glucose mobilization mechanism may become so affected that diabetes

appears, while in others the sympathetic ganglia become so facilitated, so trained, that the resulting excessive flow of action currents to the walls of the bloodvessels of the extremities leads, for instance, to Raynaud's disease.

These diseases seem to be largely due to hyperactivity of the group of organs that initiate and continue the transformation of energy. Therefore, diseases which are due to pathologic education or facilitation and exhaustion may be termed kinetic diseases.

If our reasoning is correct, and if our premises are established, then neurocirculatory asthenia, hyperthyroidism, peptic ulcer and diabetes belong to the group of so-called kinetic diseases—where there has been bred a sustained, abnormally high activity of the entire brain-adrenal-sympathetic system. The pathologic, emotional states leading up to hyperthyroidism, neurocirculatory asthenia or peptic ulcer may be regarded as similar to "fixed ideas" which produce a pathologic activation of one or more parts of the neuroglandular system.

Just as pathologic education or facilitation may lead to one or another of these kinetic diseases, so education and training may prevent or in certain cases may even cure these diseases. In too many cases, however, the pathologic physiology is so established that training and education must be aided by mechanical interferences with the facilitated mechanisms. Thus a mild case of hyperthyroidism may be cured by a sufficient period of rest; a peptic ulcer may be quieted by rest and diversion. But a return to the customary—too often abnormal—activities of life is almost certain to result in recurrence.

We have, therefore, applied the decisive test of the clinic to our conception of these kinetic diseases by lessening the power of the adrenal-sympathetic system. To this end we have performed 350 operations on the adrenal glands (53 adrenalectomies and 297 denervations).

It should be emphasized that, in the presence of psychoses, neurasthenia, or any condition in which the seat of disturbance is in the brain, adrenal denervation is contraindicated. These are not kinetic diseases and the adrenal-sympathetic system is not involved.

Since epilepsy involves rhythmic hyperactivity of the entire energy system—nervous system, muscular system and glandular system, and since the execution of such a body-wide activity involves the glands that govern energy as well as the brain and nerve ganglia, one might expect that denervation of the adrenal glands and the excision of nerve ganglia might mitigate the severity of the attacks; might convert a major into a minor epilepsy, and possibly might even effect a cure. Even if it were possible only to convert attacks of grand mal into those of petit mal, it would be well worth while. We have treated 46 cases of epilepsy by various types of dekineticizing procedures, 29 by denervation. Sixty per

cent have shown improvement or cure, while in 7 cases the operation has been performed too recently for any judgment as to the results.

Our total series includes 129 cases of neurocirculatory asthenia with improvement or cure in 93% of the uncomplicated cases; 84 of hyperthyroidism with cure in 100%; 40 of peptic ulcer with improvement or cure in 96%; and 11 cases of diabetes. In all of the cases of diabetes, hyperthyroidism was present also and as one would expect, with the cure of the hyperthyroidism the diabetes was ameliorated or cured.

In 9 cases of polyglandular disease or endocrine imbalance manifested especially by hirsutism and obesity, denervation has been followed by disappearance of the hypertrichosis and restoration of a normal habitus.

Summary. We have proposed a pathologic functional state of the brain-thyroid-adrenal-sympathetic system as the primary cause of a group of diseases occurring especially in civilized man. We have drawn attention to the energy characteristics that distinguish man. We have emphasized the fact that the brain and the sympathetic nervous system and the glands are indissolubly linked together in function; that the one component of the neuroglandular system that can be normally and pathologically conditioned is nerve tissue, that is, the brain and sympathetic nervous system; that the glands cannot be so conditioned; that the brain and the sympathetic system can be conditioned only with the collaboration of certain hormones and that in the case of civilized man the rise especially of the thyroid gland has so facilitated the conditioning of the brain that man owes his distinctions and his diseases to this unique collaboration. In support of this conception, there are offered the clinical results of the application of this principle in 350 cases of hyperkinetic diseases improved by dekineticizing procedures.

BOOK REVIEWS AND NOTICES

CONCEPTION PERIOD OF WOMEN. By DR. KYUSAKU OGINO, Head of the Gynecological Section of Takeyama Hospital, Niigata, Japan (Nippon). English Translation by Dr. YONEZ MIYAGAWA, Director of Government Institute for Infectious Diseases, Tokyo Imperial University, Hongooku, Tokyo, Japan. Pp. 94; 22 tables. Harrisburg: Medical Arts Publishing Company, 1934. Price, $1.00.

THE Thesis: Ovulation time is from the 16th to the 13th day before the next coming menstruation, and the life duration of the ovum not fertilized is less than two days. Spermatozoa in the uterus and tubes retain for not over three days their ability to fertilize an ovum. The period of possible conception for women is therefore within the 8 days from the 19th to the 12th before the oncoming menstruation, whatever the length of the menstrual cycle. Exceptions to these findings are so rare as to be unimportant in practical life.

Comment: The author is very sure of these conclusions, presents them in convincing manner, with much scientific data, and a considerable mass of human record material. The author and the publisher claim an altruistic attitude toward a needy public. The Rhythm, by Latz, and The Sterile Period in Family Life, by Coucke and Walsh are other attempts to present for practical use this physiology worked out by Ogino, and by Knaus of Austria. Dr. A. G. Miller of Hobart, Indiana, accepts this thesis, and is quoted at length in this book.

If the theory proves to be fact, curiously delayed in coming to light, we predict great advantage from its application. If it proves too good to be true, and does not work in practice, hopeful multitudes will be disillusioned if not desperate. Other published medical evidence, notably a series of 1432 dated conceptions collected by Dickinson & Bryant, show a high fertility during the 5 to 7 days just after menstruation but before Ogino's 8 fertile days in midmonth. This would be explained by longer life for the sperm cell than Ogino has found. There is general agreement among all students of fertility on the existence of a practically sterile period for the 9 to 11 days after ovulation and before the next menstruation. But there appear to be few American physicians willing yet to advise patients to trust a safe week just following menstruation. L. D.

AMEBIASIS AND AMEBIC DYSENTERY. By CHARLES F. CRAIG, M.D., M.A. (HON., YALE), F.A.C.P., F.A.C.S., Colonel, United States Army, Retired, D.S.M., Professor of Tropical Medicine, and Head of the Department of Tropical Medicine, School of Medicine, Tulane University of Louisiana, New Orleans, etc. Pp. 315; 54 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $5.00.

THE book opens with an introductory chapter which includes a brief history of the disease, and the parasite, and the present geographic distribution. Then follow, in the order listed, sections on Etiology, including discussion of the morphology and life cycle of the parasite, on Epidemiology, Pathology, Symptomatology, Complications and on Diagnosis; the last named containing extended consideration of complement-fixation tests and culture media. Prognosis, Prophylaxis and Treatment are discussed in

two final chapters. Papers to which reference is made are listed at the end of each chapter. Authors and Subjects are indexed separately. In general, illustrations are well chosen; but several which are intended to show tissue reactions and others of stained ameba are of little value. Also, available material does not entirely support the opinion that Endamœba histolytica is an obligate tissue parasite; nor does the acknowledged efficacy of amebicidal drugs allow treatment to proven cure of all who are infected. On the whole, however, the book is a reasonably complete and up-to-date discussion of a subject which probably has attracted more attention recently than it deserves. H. R.

THE RADIOLOGY OF BONES AND JOINTS. By JAMES F. BRAILSFORD, M.D. (B'HAM), M.R.C.S. (ENG.), Radiological Demonstrator in Living Anatomy, The University of Birmingham; etc. Pp. 500; 310 illustrations. Baltimore: William Wood & Co., 1934. Price, $9.00.

IN this volume the author gives a comprehensive survey of the radiology of the bones and joints. Each regional portion of the skeleton is considered individually. Reference is made to the ossification, the normal anatomy and anomalous development of the part, in addition to a description of the numerous pathologic processes to be encountered. A few pertinent facts regarding roentgenologic technique are also included. References to the literature are quite numerous and a long bibliography is given at the end of the book. The text is amply illustrated by reproductions of roentgenograms of excellent quality.

The subject matter is well presented, clear, concise and quite complete as regards the many pathologic conditions which may affect the human skeleton. However, the attempt to deal with a subject of such vast proportions in a single volume has made the reference to the individual disease, of necessity, very brief and at times too sketchy to be of real value. As a quick and ready reference for the busy radiologist in his daily contact with diseases of the bones and joints, this work will find its greatest mission. K. K.

THE PATIENT AND THE WEATHER. VOLUME III. MENTAL AND NERVOUS DISEASES. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 375, lithographed; 192 illustrations. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934. Price, $5.00.

THIS, the third of a series of volumes on the relation of the weather to disease, presents the neuropsychiatric viewpoint and gives detailed observations for the use of investigators.

Part I. Interesting chapters are devoted to Focal Reaction in the Psychoses; Oxidation; Malformations; Mental Superiority, Insanity and Inferiority; Seasonal Conception and Suicide. Part II. Psychiatric Episodes and the Meteorological Background; Interrelation of Clinical Status, Blood Chemistry and Meteorological Environment of Eighteen Psychiatric Patients. Part III. Multiple Sclerosis; Tabes and Paresis; Poliomyelitis and Meningitis.

As delineated by these authors, the effects of meteorologic conditions may possibly be so far-reaching as to affect the ovum before fertilization and thus bear upon the future stability of the individual. A fling is taken at psychoanalysis: "In that illuminating study 'Leonardo da Vinci' Freud builds up his entire thesis on a dream of the *infant* Leonardo—a dream which Leonardo may never have had!"

Some of the subject-matter is controversial, but the research is stimulating and should prove useful. N. Y.

KREBS IM LICHTE BIOLOGISCHER UND VERGLEICHEND ANATOMISCHER FORSCHUNG. By MED. DR. JOS. LARTSCHNEIDER, Linz a. d. Donau. Volume 2, No. 1, Albuminoide, Schilddrüse, Kropf, Hypophyse, Eierstock, Adenosis. Pp. 94; 19 illustrations. Leipzig: Franz Deuticke, 1934. Price, Rm. 5.

THIS is the second pamphlet of a series, which under an appealing general title assails such doctrines as the Cell Theory, *"omnis cellula e cellula"* and so on in an unconvincing manner, aggravated by obscurities of thought, style and arrangement of material. A characteristic sentence will illustrate: the anterior lobe of the hypophysis "ist eine Drüse vom Typus des menschlichen Eierstockes, bestehend, wie dieser, aus lauter in gemeinsames, von geräumigen Capillaren durchzogenes Stroma gebetteten, nicht epithelial ausgekleideten, den Pflüger'schen Eierstockschläuchen ähnlichen Schläuchen." The illustrations, poorly reproduced from standard texts, constitute the best part of the book. E. K.

MENTAL HEALTH: PAST, PRESENT AND FUTURE. By ARTHUR HILER RUGGLES, M.D., Superintendent of Butler Hospital, Providence, R. I. Pp. 104. Baltimore: The Williams & Wilkins Company, 1934. Price $1.50.

THIS addition to the literature on Mental Hygiene tells the need of public enlightenment and of greater concerted effort among workers, if we are to stem the rising tide of mental inadequacy. Statistics have been avoided and this is well for they may, unwittingly, prove deceptive. Just to mention two of several possible errors: formerly, many unfit died through neglect; today, every nook and corner is searched and all sorts of individuals who previously escaped statistical scrutiny now swell the list of the inadequate. Surely, an absolute increase is shown, but that we have a great relative increase is doubtful. Nietzsche said this civilization would end in madness and set the example himself. Of courses the situation is bad—it always has been. But despite the deficiencies of our jungle-forebears, we are here today. N. Y.

PRACTICAL TALKS ON HEART DISEASE. By GEORGE L. CARLISLE, M.D., Associate Professor of Clinical Medicine, Baylor University, Dallas, Texas. Pp. 153. Springfield, Ill.: Charles C Thomas, 1934. Price, $2.00.

EVERY practitioner of Medicine should have this book in his library: it is essentially practical and written in the intimate manner which makes Sir James Mackenzie's and Sir Thomas Lewis' books so interesting. There is none of the confusing multitude of references which, unfortunately, fill most medical publications in this country. The order in which the subjects are presented may be criticized, as it would seem wise to follow the Nomenclature approved by the American Heart Association, namely, to present Cardiovascular Disease in the order of Etiological Factors (Congenital Developmental Defects, Rheumatic Fever, Syphilis, Hypertension, Arteriosclerosis, etc.). Carlisle makes the sound statement that *"It takes time to take a history, but it is the most important point in examining a patient for any disease, and the heart case is no exception."* Reference to venous engorgement of the cervical vessels is omitted in the first chapter, but mentioned in the second. The author locates the apex beat and left cardiac border from the nipple line in man, and the midclavicular line in women; it is more customary to locate it in centimeters from the midsternal line. I do not agree with the author that percussion of the cardiac diameters is a waste of time; but I certainly agree that considerable time should be spent on arriving at an *average blood pressure*, rather than merely making one

observation. His statement may be questioned that "A thrill always means an abnormal heart but not by any means a serious heart affliction." The summary of our knowledge of hypertensive heart disease with suggestions as to treatment, is practical and well presented. His admittedly personal enthusiasm for Small's serum and antigen of "Streptococcus cardio-arthritidis" in the treatment of rheumatic fever is not shared by most cardiologists. He says "The systolic pressure may be 200 or more and the diastolic 20, 30 or even down to zero." Certainly a diastolic pressure of zero is not compatible with life; if the diastolic pressure is determined by the fourth phase, diastolic pressure will seldom be found below 20. It is astounding that, in an otherwise accurate book, there should be the apparent confusion in the differential diagnosis between acute rheumatic heart disease and subacute infective endocarditis. The author has described embolic phenomena with an elarged spleen and red cells in the urine in acute rheumatic heart disease; of course these are diagnostic phenomena in subacute infective endocarditis. His chapter on Premature Contractions or "Extrasystoles" is a masterpiece. The consideration of Angina Pectoris might be criticized for omitting a more definite differential diagnosis between angina of effort and coronary occlusion. Under Treatment in Coronary Obstruction, no mention is made of an oxygen tent or chamber. The chapter on Cardiac Neurosis shows balance and good judgment, the book ending with the sentence "Intense fear of heart disease is more distressing than most real heart disease." In summary, this book must be classified in American medical literature as one of the major contributions on the subject of cardiovascular disease. W. S.

FIFTY YEARS OF MEDICINE AND SURGERY. An Autobiographical Sketch. By DR. FRANKLIN H. MARTIN. Forewords by WILLIAM J. MAYO, M.D., Rochester, Minn., and GEORGE W. CRILE, Cleveland, Ohio. Pp. 449; illustrated. Chicago: Surgical Publishing Company, 1934. Price not given.

"A CONSTRUCTIVE dreamer" and "one of the most distinguished of American surgeons," as he is called by G. W. Crile and W. J. Mayo in the two Forewords, Franklin Martin should have interesting things to tell us. His two major achievements, the creation of a great medical journal "Surgery, Gynecology and Obstetrics" and the founding of the American College of Surgeons, are covered in 6 and 102 pages respectively; yet the description of the tribulations and success of the College—history in the making—is none too long. Nor will it be as interesting to most readers as the earlier parts of these reminiscences, telling in a simple, artless and entertaining style the professional and personal life of a rising young Chicagoan. For the author's first 30 years one must turn to the first 10 chapters of his other autobiography, "The Joy of Living." E. K.

HORMONE UND INNERE SEKRETION. (Band 19 of Wissenschaftliche Forschungsberichte Naturwissenschaftliche Reihe, Herausgegeben von Dr. Raphael Ed. Liesegang, Frankfurt a. M.) By DR. FRITZ LAQUER, Wuppertal-Elberfeld Professor an der Universität Frankfurt. Pp. 368. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 18.

IN the 6½ years that have elapsed since the first edition of this summary of the endocrine situation, the author has examined ten thousand new articles of which over six thousand have been "noticed"! For insulin alone 1245 references are given, and the thyroid, parathyroid, adrenals, hypoph-

ysis and gonads get equally generous treatment. The thymus and pineal, circulatory and intestinal hormones, and those of hypothetical nature, receive consideration in a final chapter. While such an approach necessarily produces a summary style that discourages consecutive reading, it has produced a useful guide through a devious field and a very valuable book of reference. E. K.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. Seventh Session. By PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 326; 65 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 15.

AMONG the numerous articles, chiefly on thrombosis and embolism—the topic to which this session was devoted—those by Aschoff, Dietrich and Morawitz are pre-eminent. For Aschoff, thrombosis is not due to a single cause, but rather a function of a number of variables chiefly of a physical nature. Important are the number and agglutinability of the platelets and such humoral factors as the blood velocity. For Dietrich, the relations of the blood to the vessel wall, as brought out by endothelial sensitization experiments, is of prime importance. Morawitz, from an eclectic clinical viewpoint, accepts blood and vessel wall changes of toxic, infectious and allergic nature, but emphasizes the nutritional factor. For his capillary thrombometer he claims the important ability to estimate the tendency to thrombosis from examination of blood samples. E. K.

ERBPATHOLOGIE, EIN LEHRBUCH FÜR ÄRZTE. (Band 18 of Medizinische Praxis, Sammlung für Ärztliche Fortbildung. Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme, Prof. Dr. K. Warnekros.) By DR. O. FREIHERR VON VERSCHUER, Ausserordentlicher Professor der Universität Berlin und Abteilungsleiter am Kaiser-Wilhelm-Institut für Anthropologie, menschliche Erblehre und Eugenik, Berlin-Dahlem. Pp. 213; 32 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 8.

THIS 18th volume of a series devoted to practical postgraduate medical education tackles a difficult subject. To bridge the gap between the scientific and practical aspects of heredity in disease, the first half of the book gives a none-too-clear exposition of Mendelism, Mutations, Constitution and Race-pathology. In the second half is found an alphabetical list of diseases in which heredity may play a part. So many are included that often they have to be dismissed with some such statement as: "Athetosis has been observed in families." A final section of 40 pages endeavors to apply Erbpathologie to the etiology, pathogenesis and treatment of disease. E. K.

THE SPASTIC CHILD. A Record of Successfully Achieved Muscle Control in Little's Disease. By MARGUERITE K. FISCHEL. Pp. 97; 2 illustrations and 14 figures. St. Louis: The C. V. Mosby Company, 1934. Price, $1.50.

THE author of this book for lay readers describes her methods, many of them self-devised, for combating the various manifestations of Little's disease in her son from his infancy to his sixteenth year. The special training program included physical, educational, and psychological approaches. The text is biographical and is intimately individualized. Although the necessity for courage and patience is quite properly emphasized,

many generalizations drawn by the author are hardly acceptable. Some of her methods, indeed, would be ineffectual or even harmful if applied indiscriminately in more severely affected cases of Little's disease or in spastic afflictions whose courses are progressive rather than stationary or regressive. The book should offer hope and encouragement to parents, but as a technical guide to the management of spastic children generally it is not to be recommended. M. C.

MANUAL OF CLINICAL LABORATORY METHODS. By PAULINE S. DIMMITT, PH.G., Medical Technologist for the Stout Clinic, Sherman, Texas, etc. Pp. 156; 36 illustrations, including 7 colored plates. Philadelphia: F. A. Davis Company, 1934. Price, $2.00.

THIS little manual presents the usual technical steps employed in a hospital laboratory, including the phenolsulphonephthalein and Van den Bergh tests, the icteric index and the Friedman tests for pregnancy, and for the diagnosis of Hydatidiform Mole and chorionepithelioma.

While brevity is always desirable the subject matter in this manual seems to have been too briefly considered. For example, the whole discussion on human parasites is in four sentences. Often only a single procedure is outlined for an important examination and here the choice of test may be questioned by many. An example of this is the selection of a drop method (watch-glass and glass bead) for determining the coagulation time of blood.

Only the steps in performing the various tests are given. The sources of error are not discussed and reasons for important steps are omitted. To use this manual one should already have an excellent knowledge of the subject matter to adjust an error or overcome other difficulties that a technician very often meets. J. B.

SYNOPSIS OF GENITOURINARY DISEASES. By AUSTIN I. DODSON, M.D., F.A.C.S., Professor of Genitourinary Surgery and Genitourinary Surgeon to the Hospital Division, Medical College of Virginia. Pp. 275; 111 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $3.00.

A MOST exceptionally complete, accurate and safe compendium of the entire field of urology. Its 14 chapters are equally thorough, though brief, and present in each instance modern thought on etiology, pathology, diagnosis and treatment. It is essentially a student's guide and a handy reference to the diagnostic methods with which the physician in practice should be familiar. A. R.

CLINICAL PATHOLOGY OF THE JAWS. By KURT H. THOMA, D.M.D., Charles A. Brackett Professor of Oral Pathology in Harvard University; Oral Surgeon to the Brooks Hospital, etc. Pp. 643; 423 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $9.00.

THE endeavor of the author "has been to produce a complete work, including all malformations, diseases, and neoplasms of the jaw." It was designed as a textbook for students as well as a reference book for investigators and practitioners. Illustrations are numerous; the photomicrographs excellent. Some of the reproductions of gross specimens, which are less satisfactory should be omitted or improved in a second edition. In their present form they are of little aid in recognizing the condition described.

The clinical aspects are made more realistic by the inclusion of case histories, following the lead of Cabot and Moral (Einführung in die Klinik

der Zahn- u. Mundkrankheiten, Leipzig, 1920). The manner in which the subject matter is treated will go far toward demonstrating the indispensability of pathology in surgery. Thoma's experience in surgery and interest in pathology warrant that careful attention be given to his opinion. Most of the conditions described are either never or very rarely seen by the general practitioner of dentistry. If occasionally he feels oppressed by the monotony of his work, he will be refreshed by spending a few half-hours over this work which deals with a related if somewhat novel field.

The Reviewer is curious about two omissions. In the chapter dealing with fractures of the jaws, no consideration is given to the recent monograph by Ivy and Curtis (Fractures of the Jaws, 1931, Lea & Febiger, Phila.). Likewise it is hard to understand how Dorrance's views (Operative Story of Cleft Palate, 1933, Saunders, Phila.) can be completely disregarded in any discussion of cleft palate and harelip.

Typography and general physical make-up are in every respect admirable.

J. A., JR.

GRACIAN'S MANUAL. By DR. MARTIN FISCHER, Professor in the University of Cincinnati. Pp. 305; 2 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $3.00.

DR. FISCHER'S translation of these much translated aphorisms has the merit, mostly lacking in other translations, of going back to the original text. Its "clipped" apostrophic style and content, well preserved in the translation, may be illustrated by such excerpts as: "Do not be a scandal sheet. Much less be esteemed one." In evaluation, to follow the golden mean that Gracian recommends, these aphorisms may be regarded as characteristically Jesuitical, expressing a number of high ideals as well as sound truths, many of which we are slow to admit publicly even in the nineteen thirties.

E. K.

RESEARCHES IN CANCER: PART I (1896–1921: 1922–1932). By CALEB WYAND GEETING ROHRER, B.Sc., Shenandoah College, Va.; M.D., College of Physician and Surgeons of Baltimore, Md.; M.A. and Ph.D., Illinois Wesleyan University, Ill. Pp. 144; 22 illustrations. Baltimore: The Brentwood Printing Co., 1934. Price, $5.00.

HAVING survived "repeated rejections by astute editorial boards," the essays that compose this book have now been privately printed. They elucidate the author's theory of cancer, *i. e.*, that premature birth, the primary cause of cancer, is responsible for the groups of immature cells which, in line with Cohnheim's theory, develop into either benign or malignant neoplasms. An increased supply of oxyhemoglobin to these "fetal imperfections" is regarded as the exciting cause. On this basis, the author believes that he has obtained good results in treating 13 cancer cases with a glycerinated suspension of fetal tissue. No evidence is included to support his views.

E. K.

DIABETIC MANUAL FOR PATIENTS. By HENRY J. JOHN, M.A., M.D., F.A.C.P., MAJ. M.R.C., Director of the Diabetic Department and Laboratories of the Cleveland Clinic. Pp. 232; 47 illustrations. Second edition. St. Louis: The C. V. Mosby Company, 1934. Price, $2.00.

IN this edition the diet lists have been fully revised using protein, fat and carbohydrate in the proportions commonly prescribed today. Fewer diets are listed in greater variety. Chapters have been added on Marriage and Summer Camps for Diabetic Children. The feature of the book continues to be a clear presentation of the disease and its management which should encourage the intelligent diabetic.

F. L.

NEW BOOKS.

The Advance of Science. Edited by WATSON DAVIS, Director, Science Service, Washington. Pp. 400; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1934. Price, $3.50.

The Constitution and Its Reaction in Health. By T. E. HAMMOND, F.R.C.S., Assistant Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 160. London: H. K. Lewis & Co., Ltd., 1934. Price, 7/6.

Gracian's Manual. By DR. MARTIN FISCHER, Professor in the University of Cincinnati. Pp. 305; 2 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $3.00. (Review, p. 287.)

Treatment by Diet. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago; Formerly Consulting Physician, The Mayo Clinic. Pp. 615; illustrated. Philadelphia: J. B. Lippincott Company, 1934. Price, $5.00.

The Physical and Mental Growth of Prematurely Born Children. By JULIUS H. HESS, M.D., Professor of Pediatrics, College of Medicine, University of Illinois; Attending Pediatrician, Illinois Research, Cook County and Michael Reese Hospitals; GEORGE J. MOHR, M.D., Director, Pittsburgh Child Guidance Center, etc., and PHYLLIS F. BARTELENE, PH.D., Psychologist, Cook County Juvenile Court, Chicago; Resident Psychologist, Institute for Juvenile Research. Pp. 449; 90 illustrations and 161 tables. Chicago: University of Chicago Press, 1934. Price, $5.00.

The Brain as an Organ. Its Postmortem Study and Interpretation. By FREDERIC WERTHAM, M.D., Formerly Associate in Psychiatry, Johns Hopkins Hospital and Medical School, etc., and FLORENCE WERTHAM, Formerly Charlton Fellow in Medicine, Johns Hopkins University, etc. With an Introduction by ADOLF MEYER, M.D., Psychiatrist-in-Chief, Johns Hopkins Hospital. Pp. 538; with text illustrations and 166 plates. New York: The Macmillan Company, 1934. Price, $7.50.

Lectures on Medical Electricity. By ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.M.R.E. (CAMB.), F.R.C.P., Medical Officer in Charge, Electrical Department, and Lecturer on Medical Electricity, St. Bartholomew's Hospital, etc. London: Henry Kimpton, 1934. Price, 6/-

Transactions of the American Otological Society, Inc., Volume 24, Sixty-seventh Annual Meeting, Atlantic City, April 6 and 7, 1934. Pp. 316; illustrated. Published by the Society, 1934. (No price given.)

Principles in the Treatment of Inflammation. By T. E. HAMMOND, F.R.C.S., Assistant Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 209. London: H. K. Lewis & Co., Ltd., 1934. Price, 10/6.

An Atlas of the Commoner Skin Diseases. By HENRY C. G. SEMON, M.A., M.D. (OXON.), M.R.C.P. (LOND.), Physician for Diseases of the Skin, Royal Northern Hospital. Photography under the Direction of ARNOLD MORITZ, B.A., M.B., B.C. (CANTAB.). Pp. 221; 103 colored plates. Baltimore: William Wood & Co., 1934. Price, $12.00.

The New-born Baby. A Manual for the Use of Midwives and Maternity Nurses. By ERIC PRITCHARD, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Medical Director, Infants Hospital London; Pediatrician to Queen Charlotte's Maternity Hospital, etc. Pp. 272; 9 illustrations. London Henry Kimpton, 1934. Price, 4/6.

International Clinics, Vol. IV, Forty-fourth Series, 1934. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 collaborators. Pp. 326; illustrated. Philadelphia: J. B. Lippincott Company, 1934. (No price given.)

This volume maintains the improved standard set in the recent reorganization of this journal. The 9 medical articles comprise a little more than half the total.

The Vitamin B Requirement of Man. By GEORGE R. COWGILL, PH.D., Associate Professor of Physiological Chemistry in Yale University. Pp. 261; 8 illustrations, 81 tables and 8 charts. New Haven: Yale University Press for the Institute of Human Relations, 1934. Price, $4.00.

Food and Health. By HENRY C. SHERMAN, Mitchill Professor of Chemistry, Columbia University. Pp. 296. New York: The Macmillan Company, 1934. Price, $2.50.

Body Mechanics. In the Study and Treatment of Disease. By JOEL E. GOLDTHWAIT, M.D., LL.D., Member of Board of Consultants, Massachusetts General Hospital, etc., LLOYD T. BROWN, M.D., Instructor Orthopedic Surgery, Harvard Medical School, LORING T. SWAIM, M.D., Instructor Orthopedic Surgery, Harvard Medical School, and JOHN G. KUHNS, M.D., Assistant in Orthopedic Surgery, Harvard Medical School. Pp. 281; 99 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, $4.00.

Cold Spring Harbor Symposia on Quantitative Biology, Volume 2. Pp. 284; illustrated. Cold Spring Harbor, L. I., N. Y.: The Biological Laboratory, 1934. Price, $3.35.

Researches in Cancer: Part One (1896–1921; 1922–1932). By CALEB WYAND GEETING ROHRER, B.Sc., Shenandoah College, Va.; M.D., College of Physicians and Surgeons of Baltimore, Md.; M.A. and PH.D., Illinois Wesleyan University, Ill. Pp. 144; 22 illustrations. Baltimore: The Brentwood Printing Company, 1934. Price, $5.00. (Review, p. 287.)

Die Neurologie des 1.–7. Jahrhunderts N. Chr. Eine historisch-neurologische Studie. By DR. WALTER CREUTZ, Oberarzt an der Prov.-Halund Pflegeanstalt, Düsseldorf-Grafenberg, und der Psychiatrischen Klinik der Medizinischen Akademie, Düsseldorf. (Band VI of Sammlung Psychiatrischer und Neurologischer Einzeldarstellungen.) Herausgegeben von Prof. DR A. BOSTROEM, Kömesberg i. Pr., und Prof. DR. J. LANGE, Breslau. Pp. 106. Leipzig: Georg Thieme, 1934. Price, M. 7.80.

NEW EDITIONS.

Surgical Applied Anatomy. By SIR FREDERICK TREVES, BART. Pp. 720; 174 illustrations, including 66 in color. Ninth edition revised by C. C. CHOYCE, C.M.G., C.B.E., B.Sc. (N.Z.), M.D. (EDIN.), F.R.C.S. (ENG.), Professor of Surgery, University of London; Director of the Surgical Unit, University College Hospital Medical School, etc. Philadelphia: Lea & Febiger, 1934. Price, $4.00.

This ninth edition continues as one of the most useful compendiums on an essential subject, the text having been brought up to date by Professor Choyce. The surgical anatomy is discussed according to the various regions of the body: diagrammatic and schematic drawings illustrating the essential facts. L. F.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
I. S. RAVDIN, B.S., M.D.,
J. WILLIAM WHITE PROFESSOR OF SURGICAL RESEARCH, UNIVERSITY OF PENNSYLVANIA,
AND
C. G. JOHNSTON, M.S., M.D.,
INSTRUCTOR IN SURGERY, UNIVERSITY OF PENNSYLVANIA,
PHILADELPHIA, PA.

ACUTE APPENDICITIS.

For the last decade there has been a renewed interest in the subject of acute appendicitis and during the past year a number of very interesting papers have appeared on this subject. It is realized that both the incidence and mortality are increasing and that there is a wide disparity in the results of treatment in certain large medical centers and in the country as a whole.

From the time that Mestivier[1] of France, in 1759, demonstrated by autopsy the first recorded case of disease of the appendix to within 25 years of the appearance of Reginald Fitz's[2] paper in 1886, there was a total of 141 cases of this disease recorded in medical literature. The Willard Parker[3] procedure, first advocated in 1867, consisted solely of incision and drainage for appendiceal abscess. Kelly[4] states that "To Thomas G. Morton of Philadelphia belongs the credit for the first successful operation for the removal of the appendix, deliberately undertaken." The date was April 27, 1887.

John B. Deaver[5] has very clearly outlined the early history of this subject in this country. He referred to the differences of opinion which existed in regard to the treatment of appendicitis as follows: "Not only was the controversy as to the surgical or non-surgical treatment of appendicitis the occasion for unpleasant personalities, that were as galling as they were undignified and unjust, but it was the cause of bitter enmities that often persisted during a whole lifetime. From the beginning of my recognition of the importance of the potential mischief resident in the appendix, I was one of the ardent advocates for its removal in acute cases of inflammatory disease of the organ, and later on also for its routine removal in many diseases of other abdominal viscera. Arrayed with me on the affirmative side of the question were men like Morton, Pepper, Osler, the two Prices of this city, Maurice Richardson, John Murphy, and others who have passed on to their

reward; and still others, McBurney, Keen, the Mayos, Ochsner, and many more who are happily still keeping alive the good name of surgery in America, and whom I deem it a privilege to count among my friends.

"Prominent among contemporary opponents to early operative treatment of appendicitis was Nicholas Senn, who on one occasion at a meeting of the American Medical Association did me the honor of declaring in public that a surgeon holding the views I was advocating was so questionable an ornament to the profession that he ought to be deprived of his privileges and of his diploma. My answer to his insinuation I am afraid, was about as flattering to my denouncer as was his accusation to me. A few days after Dr. Senn's arrival home he wrote me: 'While we fight like bulls within the arena, behind the scenes we are peaceful lambs; I am very anxious to have you address the Senn Festsschrift Medical Society.' This is by no means an extreme nor an isolated example of the bitterness that marked the stormy controversy at its height. But the atmosphere has been cleared since those days, and the primary question no longer is whether to operate but rather when and perhaps how to operate."

In 1914 the late John B. Murphy[6] stated that the mortality from appendicitis was far too high and one year later Haggard[7] of Nashville agreed with him when he stated that "hospital reports for the past year show that the average mortality in appendicitis in all stages of the disease in those reported hospitals is about 20 per cent." A decade later A. Murat Willis,[8] from a study of vital statistics, called our attention to the increase in the mortality after operations for appendicitis since the Word War. He called attention to a rise in the appendicitis death rate from 11 per 100,000 deaths in 1900 to 14.4 per 100,000 in 1921 and concluded: "Destructive criticism is of small value unless it prepares the way for subsequent improvement. The presentation of facts which has just been made indicates that something is radically wrong with the modern surgical treatment of certain important conditions. Can this be remedied? It would seem that the first step would be the appointment by the American College of Surgeons of a commission, composed of the leading surgical teachers of this country; the function of this commission being to direct a thorough investigation of the whole question, with a view to effecting some degree of standardization of the methods of treatment of these diseases, regarding which, at present, there seems to be such a complete lack of agreement."

In this paper were also reported statistical data from several clinics as follows:

	Death rate percentage.
"Ochsner, Professor of Surgery, University of Illinois, reported in Clin. Surg., 1912, from 1901–1905	4.1
Personal Communication, September, 1924	2.0
Deaver, Professor of Surgery, University of Pennsylvania, reported in Ann. Surg., June, 1924.	
Using method of Gatch, 1901–1905	10.5
Using the Ochsner method, 1910–1919	3.9
Gatch, Professor of Surgery, Indiana University, reported in Ann. Surg., 1924, June, rate for 1924	8.7"

In 1927 the late Ashley P. C. Ashhurst[9] reported on 247 patients on whom he personally had operated and in whom drainage was necessary. The mortality was 13.7%.

Two years later John O. Bower began the first of a series of surveys of the mortality from operations for acute appendicitis in 28 of the larger hospitals of Philadelphia. These surveys have been continued every year since then. During this period there has been an intensive educational campaign on the subject of appendicitis and its complications, in which the Philadelphia Association of Retail Druggists has coöperated. The following table gives the data compiled by Bower[10] over a 6-year period:

Acute Appendicitis, Philadelphia Hospitals (Bower).

Year.	Number of cases.	Number of deaths.	Per cent mortality.
1928–1929	5121	306	5.97
1930	3095	149	4.81
1931	3142	138	4.39
1932	3546	122	3.44
1933	3783	134	3.54

Bower[10] gives the causes for the increasing mortality as (1) delayed hospitalization, (2) less competent management of spreading peritonitis, (3) increase in the administration of laxatives.

The results of the Philadelphia campaign Bower gives as follows: "The family physician has benefited by the campaign. Unfortunately, the percentage of physicians who follow their patients to the operating room is too small. Early pathologic changes, which can be correlated with symptoms and signs, can be seen in no other way.

"The internes have profited. This is shown by the improvement in clinical records—better histories are usually accompanied by more careful physical examinations.

"The anesthetists play a part in the making of a clinical record which has an indirect bearing on the average case, although they have not been affected directly by the campaign.

"The pathologist, however, has been affected. Fewer cases of peritonitis—fewer deaths from peritonitis.

"The nurses have benefited and they have been excellent propagandists in the spreading of information relative to earlier hospitalization and the dangers of administration of laxatives.

"The surgeons have profited; patients have been admitted earlier—the number of cases of Spreading Peritonitis admitted have been fewer. The following table shows this improvement over a period of 5 years."

Results of Appendicitis Campaign, Philadelphia 1928 to 1933.

	1928, %.		1933, %.	
Reduction in Mortality from	5.97	to	3.54	41.0% decrease
Increase in Clean Cases from	57.04	to	73.75	29.5% increase
Decrease in Mortality of Spreading Peritonitis from	33.95	to	24.61	27.61% decrease

Although all writers are not in complete agreement with the use of vital statistics as a method of collecting data on the death rate from appendicitis, even Walker[11] who takes exception to some of Willis'[12] statements agrees that the mortality is still too high since he states: "We do not wish to avoid the issue that more individuals have died as a result of the endeavor to cure appendicitis during recent years

than previously." It is generally agreed that two important factors contributing to the present high death rate are delay in operation and catharsis.

Acute appendicitis is a surgical disease. There remain then only three factors which may delay operations: (1) failure of the patient to consult his physician; (2) failure of the physician to diagnose the lesion, and (3) procrastination by the physician once the lesion has been diagnosed. Willis[12] has very aptly stated that "provided a good hospital and a capable surgeon are available and a diagnosis of acute appendicitis has been made, prompt operation is the treatment."

The diagnosis of acute appendicitis is not always a simple matter. Too often the physician waits until a textbook picture is present before consulting the surgeon, a time at which perforation may have already occurred. The symptoms will continue to vary as long as the virulence of the infection varies and as long as the quantitative reaction to infection varies in different individuals. Many more patients have been lost as the result of a delay in operating than have been lost from an occasional error in the diagnosis. The surgeon is seldom responsible for this delay.

It may be said that the increase in mortality is associated with an increase in the number of operations for appendicitis. That there has been an increased incidence is without question, for Walker[11] found a rise of 277% in certain districts of New England for the 4-year period 1927 to 1930 over the period of 1907 to 1910. It would appear, therefore, that the disease is being diagnosed with increasing frequency, at least in some sections. If this is true the increase in the mortality rate must be associated with an increase in the number of operations being done by inexperienced and poorly qualified surgeons.

Bower[10] recently suggested "That the surgical service in our hospitals as it pertains to acute appendicitis be modified to the extent that the junior members of the surgical group manage the clean cases but that a consultation be held with the chief of service regarding the management of the perforative or suspected perforated case. Neither a watchful-waiting nor a drastic policy is advocated, but a request that the 12 or 15% of patients admitted to our hospitals with Spreading Peritonitis, who have only one chance in four of living, be given the benefit of all that the service affords in the matter of surgical judgment and experience. Wisdom in surgery usually increases with experience, but not always. The clinical records reviewed showed that a man may spend decades managing Spreading Peritonitis and still have a mortality of 65%. The associate of the surgical service should concentrate on the pre-operative diagnosis of Spreading Peritonitis; his chief should concentrate on management and be willing to pass along to his associates the knowledge he has gained in the managing." The suggestion which Bower made is a good one and if followed closely could not but result in a lower operative mortality.

The mortality of simple acute appendicitis is negligible. As Ashhurst[9] and Shipley and Bailey[13] have said, most deaths occur in the delayed group. Sworn and Fitzgibbon[14] have recently reported the data on 2126 patients with acute appendicitis operated on in St. Thomas' Hospital, London, from 1920 to 1929. There were 231 cases of diffuse peritonitis from appendicitis of 1, 2, 3, or 4 days' duration with a mor-

tality of approximately 19%. Of 487 cases of abscess the mortality was less than 4%, and in 1340 cases without peritonitis the mortality was only 1.71%. These data could be repeated by reviewing the statistics found in any surgical clinic, since there is no disagreement with the statement that delay in hospitalization results in an increase in the number of patients admitted in the various stages of peritonitis.

That the mortality with or without peritonitis can be reduced if careful attention is given to the various details of pre-operative treatment, the judicious selection of anesthesia, the careful planning of the operation and exacting postoperative care is without question.

Many years ago Clark[15] discussed the results obtained in peritonitis after the use of large doses of morphin. Later Ochsner[16] suggested that in the late cases of peritonitis from appendicitis, operation be delayed until the peritonitis was localized. In the interim he suggested fluid by rectal drip, the maintenance of the Fowler position and morphin.

It is agreed that in the early cases early operation is indicated. In the late cases, however, there appears to be no such unanimity of opinion. Tait[17] believed that purgation rather than rest with morphin was indicated in peritonitis. Stockton[18] found the use of morphin helpful, while Bovée[19] in an article published in the same issue of the same journal took the opposite point of view. For years John B. Deaver subscribed to and was one of the most ardent advocates of the Alonzo Clark-Ochsner method of treatment in spreading peritonitis.

The matter has not as yet been finally settled. Even among those surgeons who believe that the delayed method of treatment in spreading peritonitis results in a lower mortality there is no agreement as to the time limit for the immediate and the delayed operation. Thus, Arnheim and Neuhof[20] operate immediately on all patients having a 24-hour history, while after this time they frequently delay operation. And yet rupture with a rapidly spreading peritonitis may occur 2 hours after the onset of symptoms.[21] In a discussion before the Royal Society of London, Ryle[22] favored deferring operation in some of the late cases and immediate operation in others. Rayner[23] delayed operation only long enough to improve the patient's condition, while Morley-Fletcher[24] quoted Sir James Berry as saying that "he deprecated the present practice of operating immediately in all cases of appendicitis. He believed that in acute appendicitis in children immediate operation was indicated. We believe this point of view is well taken, since in children localization does not take place so readily, and it is more difficult with them to withhold fluids by mouth for long periods as is often necessary when the delayed treatment is used. Colley-Davies[25] on the other hand was opposed to a delay in the operation when peritonitis was present which he stated would "put the profession back 20 years in the period of generalized peritonitis, pylephlebitis and subphrenic abscess." Cope[26] believed that delay was often advisable in patients with spreading peritonitis.

Little would be gained by further reviewing the opinions of various writers. The reviewers believe in the delayed treatment in the presence of generalized peritonitis; except in children as above indicated. In such cases the administration of adequate doses of morphin prevents overdistention of the small bowel. It assists in maintaining the tonus of the bowel and by controlling distention prevents disturbances in the

circulation of the intestine. The work of Plant and Miller[27] and of Orr[28] well illustrate these facts. The use of suction drainage, as described by Wangensteen,[29] of the Fowler position and the intravenous administration of sodium chlorid and glucose all aid in permitting the operation to be delayed until such time as localization has occurred.

Anesthesia.—Several years ago Foss[30] stated that the mortality after operations for acute appendicitis was reduced 50% since the routine use of spinal anesthesia. Arnheim and Neuhof[20] advocate the use of avertin and nitrous oxid and oxygen. They believe that the shock which may result from spinal anesthesia lowers general resistance to infection and thus invites the spread of the infection. There appears to be no basis for the foregoing statement and the reviewers are not in agreement with it.

Rayner[23] favored spinal or nitrous oxid and oxygen rather than ether or chloroform anesthesia. Morley-Fletcher[24] believed spinal anesthesia was superior to general anesthesia. The relaxation afforded by spinal anesthesia permits of operation with a minimum of trauma. The extensive use of gauze packs is not required. Postoperative pulmonary complications are not so frequent and the anesthetic is without effect on the liver parenchyma. In the early cases it should make little difference which anesthetic is used; but in the patients with a diffusing peritonitis, spinal anesthesia would seem to be the anesthetic of choice.

Incision.—It is our opinion that the incision suggested many years ago by McBurney is still the best one to use in cases of acute appendicitis. Arnheim and Neuhof[20] state that the majority of their patients have been operated on through a rectus splitting incision. The argument used in favor of the rectus incision is that it provides wider exposure; that the use of a routine incision is illogical; that it may make access to the appendix more difficult, and may lead to spread of the infection. These objections we believe to be largely imaginary, since the McBurney incision in the majority of instances provides the most direct access to the appendix, it can be lengthened in any direction and of all the incisions it is least likely to result in a spreading of the infection. The right rectus incision on the other hand provides direct access to the small bowel and thus favors the spread of the infection by carrying an infected focus across small bowel which may as yet be uncontaminated.

Colt and Morrison[31] reported that the mortality in their cases from 1923 to 1929 was 0.69% when the Battle incision was used and 6.05% when the paracentral incision was used. They attributed the higher mortality associated with the paracentral incision to the fact that there was greater possibility of spreading the infection when it was used.

Reid[32] has expressed an opinion in regard to the McBurney incision with which the reviewers are in complete agreement: "The author and the members of our surgical department have long ceased to have a feeling of embarrassment after making a McBurney incision for a mistaken diagnosis of acute appendicitis. With no appreciable reduction in the elapsed interval between the onset of symptoms and operation or in the use of purgatives prior to surgical treatment the death rate for all forms of acute appendicitis treated in the Cincinnati General Hospital has been reduced by 50.3% since the routine of a rectus incision was abruptly and completely changed to that of a McBurney incision." A review of statistical data reveals the important fact that the mortality

from acute appendicitis is lowest in those cities in which the McBurney incision is most widely used.

Technique. In 1901 it was suggested by Morris that in appendiceal suppuration the appendix be removed and as much of the pus be aspirated as possible, after which the abdomen be closed without drainage. Buchanan in 1910 and again in 1923[34] has reported favorable results after the use of this method. The procedure has gained more or less favor because of the incidence of intestinal obstruction following drainage of the peritoneum and the knowledge that the general peritoneal cavity cannot be drained.

Shipley and Bailey[13] in a discussion of the treatment of acute appendicitis with peritonitis state that "drainage material, especially in the lower abdomen, often causes widespread adhesions between loops of intestines, mesentery, omentum, pelvic organs and abdominal wall. The drains are soon sealed off and do not drain any considerable portion of the peritoneum." These authors advocate in early peritonitis, removal of the appendix, aspiration of free fluid and exudate and then irrigation of the contaminated area with warm normal salt solution which is then aspirated. After this the peritoneum is closed without drainage. In the discussion of Shipley and Bailey's paper Eugene Pool[35] stated that, "all accept the fact that the wound should be closed without drainage if it is reasonable, but a certain number of cases must be drained. Dr. Shipley makes a great mistake in irrigating within the peritoneal cavity. Blake advocated irrigation many years ago but he has since admitted the fact that it is a mistake."

We do not believe that irrigation is of any value. When practised through the median incision as suggested by Torek[36] considerable trauma to the serous surfaces of the bowel must result. It should be remembered that to a degree fibrinous exudate is protective and that when it is removed there remain behind large areas of denuded gut. Drainage should be practised only when a considerable amount of necrotic material is left behind. When drains are used these should be soft and should be placed along the lateral abdominal or pelvic wall.

In the postoperative period the use of a suction drainage in the presence of peritonitis is a distinct advance in treatment. It has been our experience that since this procedure was instituted postoperative jejunostomy or ileostomy for adhesive obstruction is only rarely indicated.

We have occasionally done an appendicostomy at the time of removal of the appendix in the very sick patient. The method was suggested to us by Wilson of Emporia, Kansas. Recently Jones[37] has reported the use of this procedure in late cases with the most gratifying results. Without doubt it could be used more frequently than it now is.

It is necessary that the surgeon and his staff be ever alert to the complications which may occur during convalescence. Arnheim and Neuhof[20] have rightly stated that when the patient fails to do well after operation, the surgeon should first look to the abdomen for the cause of the trouble rather than to the chest and more distant areas.

The final solution of the high mortality in acute appendicitis must depend on earlier operation. To attain this there should be an intensive national education campaign among the laity and a closer coöperation between the general practitioner and the surgeon.

I. S. Ravdin and
C. G. Johnston.

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OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.,
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINN.,
AND
H. P. WAGENER, M.D.,
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINN.

RETINITIS PIGMENTOSA.

RETINITIS pigmentosa has generally been considered to be a hereditary and familial disease, usually progressive and essentially incurable. Its etiology has not been definitely established. Its outstanding subjective

symptom is night blindness, with loss of central vision a secondary and subsequent feature. Its most prominent objective symptoms are narrowing of the retinal arteries and deposits of pigment in the retina. In most cases it is an isolated lesion. Whether all forms of pigmentary degeneration of the retina of progressive character and unknown etiology should be classified as variants of the typical retinitis pigmentosa is difficult to say. The association, at times, of apparently typical retinitis pigmentosa with nerve deafness, epilepsy, and mental deficiency has long been known. In more recent years the recognition of the Laurence-Biedl syndrome, the finding of pigmentary degeneration of the retina in certain disturbances of hepatic function, the demonstration of hemeralopia as a definite symptom of avitaminosis, and the study of the vasodilating effects of sympathectomy have led to renewed interest in attempts to arrest the progress of typical, isolated retinitis pigmentosa by treatment with various hormones, with diets high in vitamins, with vasodilating drugs, and with cervical and cervicothoracic sympathectomy.

Verhoeff's[1] histologic examination of an eye, which was removed during life and which had been blind with retinitis pigmentosa for more than 20 years, confirmed Leber's[2] opinion that the essential ocular lesion in retinitis pigmentosa is progressive degeneration of the neuroepithelium, the rods being affected first. The changes affecting the pigmented epithelium probably result from degeneration of the neuroepithelium. The choriocapillaris was normal and Verhoeff was of the opinion that obliteration of the choriocapillaris or choroidal circulation can be dismissed as a possible cause of retinitis pigmentosa. In his case there was no definite degeneration of the ganglion cells or atrophy of the optic nerve. The reduction in caliber of the retinal vessels, which is apparent ophthalmoscopically, is seemingly produced by thickening of the connective tissue of the adventitia, without any obvious microscopic reduction in the lumen. As a result of their experiments with the injection of granules of melanin into the vitreous of rabbits, Friedenwald and Chan[3] concluded that all the histologic changes in the retina in retinitis pigmentosa can be accounted for on the hypothesis of a primary lesion of the retinal neuroepithelium, with secondary, long continued infiltration of the retina with melanin granules.

Verhoeff called attention to the possibility that retinitis pigmentosa is the result of disturbance of hepatic function. In certain diseases of the liver, notably hypertrophic cirrhosis, night blindness occurs which possibly is the result of an excess of bile salts in the blood that may affect the visual purple and the rods in which it is supposed to reside. Verhoeff cited the experimental work of Sugita which indicated that the pigmented epithelium and neuroepithelium of the retina can be injured by certain constituents of the bile acting through the blood. He also quoted the investigations of Takahashi, who found the hepatic function abnormal in 12 cases of retinitis pigmentosa. Boenheim,[4] Moreau,[5] and Satanowsky[6] also called attention to the disturbance of hepatic function in certain cases of retinitis pigmentosa.

Collins[7] was of the opinion that retinitis pigmentosa was an abiotrophy of the retinal neuroepithelium, since the rods and cones belong to the class of cells which in adult life lose their power of proliferation and may, in certain cases, die early in life. Verhoeff thought that this

theory explains the facts well but offers no hope for methods of controlling the disease. A study of cases of the Laurence-Biedl syndrome throws a somewhat different light on the possible nature of this abiotrophy.

The association of adiposogenital dystrophy, mental deficiency, retinitis pigmentosa, and polydactylism has been recorded in the literature in from 40 to 50 cases. The recent cases have been grouped under the title Laurence-Biedl syndrome. The cause of this syndrome was originally supposed to be a disturbance of the pituitary gland. Later, Biedl[8] suggested that the essential factor in the production of the syndrome was the presence of an unusually high or massive dorsum sellæ which prevented the passage of pituitary secretion through the stalk to the floor of the third ventricle, as a result of which certain metabolic and genitotropic centers were affected. Ornsteen[9] advanced the hypothesis that this syndrome is dependent on a developmental defect of the ectopic zone of the prosencephalon, since, embryologically, the hypothalamus and optic chiasm take origin from the ventral segment and the end brain from the cephalic segment of this zone. This defect results in an abiotrophic condition of the infundibulum, the optic nerves, and the retina, since, according to Tilney and Riley,[10] some efferent fibers in the optic chiasm govern chemical changes in the retina and also movements in the retinal pigment cells. Weiss[11] is inclined to agree with Ornsteen's hypothesis and reports that treatment of such patients with glandular extracts, chiefly thyroid and pituitary, results in improvement of some cases. Zondek[12] called attention to the fact that a hormone from the pars intermedia of the hypophysis has been shown to affect the melanophores of frogs and also the pigment cells of fishes. He reported 4 patients with retinitis pigmentosa who gave evidence of pituitary obesity or cachexia and psychic depression. Treatment with prolan was tried, but without much success. Belskij and Jalin[13] reported 7 cases of retinitis pigmentosa with changes in the sella turcica, deposits of calcium in the bones of the hands and feet, and increased blood calcium apparently resulting from parathyroid disturbance. They stated that calcium iontophoresis was of benefit in these cases.

It has been demonstrated by a number of observers that night blindness is a rather constant symptom among patients and experimental animals who are deprived of vitamin A. The normal retina has been shown to store a large amount of vitamin A, and apparently the regeneration of the visual purple is dependent on the presence of this vitamin in the retina. The apparent increased sensitivity to light of the pigment cells of the skin and retina, demonstrated by Venzella[14] in cases of retinitis pigmentosa, may indicate a lowered capacity for the regeneration of the visual purple. Night blindness has been shown to occur among pregnant women whose diet is low in vitamin A. Henderson[15] reported a case of retinitis pigmentosa and retinitis punctata albescens in which the condition progressed markedly during pregnancy.[16] I reported a case of retinitis pigmentosa in which the field defects progressed definitely during the last month of pregnancy and returned to their previous status after the termination of pregnancy. These findings have suggested that the addition of large amounts of vitamin A to the diet might have a favorable influence on the course of retinitis pigmentosa. Levine[17] reported, however, that he had no success in a series of patients treated with large doses of cod liver oil over a con-

siderable period of time. Wilder[18] has suggested that in these cases there may be a defect in the capacity of the retina for storage of vitamin A, and that the use of a ketogenic diet might increase this storage capacity. One patient has been treated along these lines at The Mayo Clinic with apparent good results, and this method of treatment seems worthy of further trial. Satanowsky notes that the rods, and probably the cones, function through means of the visual purple, that the visual purple is soluble in bile acids and their salts, and that lack of vitamin A interferes with its regeneration. She reported 3 cases of retinitis pigmentosa in which there was disturbed hepatic function and stated that liver therapy is of benefit in these cases. Kestenbaum[19] treated a patient with ovosan to produce hyperemia of the retina, and with liver to increase retinal metabolism; he obtained favorable results.

In spite of the opinion of most histologists that interference with the retinal or choroidal circulation is not a primary factor in the pathogenesis of retinitis pigmentosa, it seems to be true that the most favorable results in the treatment of this disease have been obtained through the use of methods for the production of vasodilatation in the retina and choroid. Histologically, Asher[20] found thickening of the connective tissue of the choroid in the macular region, narrowing of the vessels with changes in their walls, marked changes in the pigmented epithelium, complete destruction of the neuroepithelium, collections of pigment in the walls and lumens of the retinal vessels, atrophy of the optic nerve, and thickening of the walls, with narrowing or occlusion of the lumens, of the vessels in the nerve head. He was of the opinion that these changes fit in better with the theory of primary injury to the capillaries of the choroid and retina than with the theory of abiotrophy of the neuroepithelium, or with that of a primary degeneration of the pigmented epithelium. Mariotti and Lugli[21] reported improvement in retinitis pigmentosa following retrobular injections of atropin, with resultant dilatation of vessels. Corrado[22] obtained improvement through the use of acetylcholin. Moreau was not successful in the treatment of 6 patients with hereditary retinitis pigmentosa by vasodilating methods, but in 2 cases in which the condition was associated with disease of the liver, marked dilatation of the vessels, with improvement in the field of vision, was produced by injection of acetylcholin into the vitreous. Wibaut[23] treated 31 patients with retinitis pigmentosa with menformon, which produces dilatation of the smaller arteries or capillaries. One patient showed marked improvement and 7 slight improvement. There was doubtful improvement in 13 cases and no improvement in 10. Von Heimburg,[24] however, found no improvement in 5 cases after the use of menformon.

Apparently the most efficient means of producing lasting dilatation of peripheral vessels is removal of sympathetic ganglions and section of the sympathetic trunks. It is generally accepted that the vessels of the retina are under the control of the cervical sympathetic nerves, and I[25] have demonstrated that dilatation of the arteries in normal retinas occurs in a high percentage of cases following cervicothoracic sympathetic ganglionectomy. Following the lead of Royle,[26] a number of operations on the cervical and thoracic sympathetic nerves have been performed in cases of retinitis pigmentosa. The results, in the main, have apparently been favorable. Royle reported 4 cases in which patients

were improved following division of the sympathetic trunk about the level of the second thoracic ganglion. In Meighan's[27] case the superior and middle cervical ganglions were removed along with the intervening trunk. In this case, as in Royle's cases, improvement in fields and vision was noted in both eyes though the operation was performed on only one side. This fact makes interpretation of the results rather difficult. Several patients have been operated on at the clinic, and the changes in the fields were far advanced. Subjective improvement was noted, but an objective widening of the peripheral fields could not be demonstrated. It would seem that the results obtained by various operators would justify a further trial of cervical or cervicothoracic sympathectomy, especially in the early stages of retinitis pigmentosa.

H. P. WAGENER.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 17, 1934

Sulphur Metabolism. A Study of a Case of Cystinuria.—JAMES C. ANDREWS and ALEXANDER RANDALL (Departments of Physiological Chemistry and Urology, University of Pennsylvania). A study has been made of the metabolism of sulphur compounds in a male cystinuric (age 14) using, as a control, a normal subject of the same age and sex.

The cystin output of the cystinuric is remarkably constant, and averages 0.09 to 0.10 gm. of cystin sulphur per day. This output is unaffected by the daily feeding of sodium bicarbonate or sodium citrate in amounts sufficient to keep the urinary pH between pH 7.0 and 7.5 although this alkalinity suffices to keep the cystin dissolved and to prevent calculus formation.

Daily administration of equimolar proportions of glycin and glutamic acid is without effect on the cystin output.

The use of a diet high in eggs (containing larger amounts of sulphur) does not raise the cystin output.

As has often been observed with other cystinurics, the present subject oxidizes cystin administered by mouth to sulphate and does not show any increase in urinary cystin output. In confirmation of the work of duVigneaud on the normal metabolic oxidation of the isomers of cystin, we find that the levo isomer is somewhat more rapidly and completely oxidized than the racemic mixture.

dl-Methionin is oxidized to sulphate to the extent of 60 to 80%; the remainder is excreted as unoxidized sulphur. In contradiction to the results reported by Brand and coworkers, we do not find that the administration of methionin to the cystinuric increases the cystin output. Direct determinations of methionin in the urine indicate that only a small proportion of the methionin which escapes oxidation to sulphate can be excreted as such. The remainder is excreted in some unknown form in which the sulphur is not oxidized to sulphate. The rate of oxidation and elimination of methionin sulphur by the cystinuric individual is much slower and more erratic than by the normal subject.

Cysteic acid, when fed to the cystinuric as well as to the normal subject, is excreted unoxidized.

The increase in the cystein content of cystinuric urines on standing, when the cystin content is determined by the Sullivan procedure, has been noted by Brand and coworkers and has been ascribed by them to the excretion of part of the cystin in the form of an easily decomposed cystin complex. Without necessarily subscribing to this explanation, we confirm the results reported by Brand. We have observed that the cystin content of a freshly voided sample can increase, even on standing 24 hours at 0° C. and when preserved with chloroform, to from 25 to 50% over its original value. This higher value is maintained for at least several months.

Liebermann-Burchard Reaction Velocities of Sterols: I. Differences Between Free and Ester Cholesterol Applied to the Determination of Cholesterol Esters. II. A Test for the Presence of Coprostenol in Plasma.—JOHN G. REINHOLD (Laboratory of Philadelphia General Hospital). Cholesterol esters and coprostenol (allocholesterol) develop color more rapidly than cholesterol when treated with acetic anhydrid and sulphuric acid. The difference in reactivity of free and esterified cholesterol is increased by low temperatures and low concentrations of sulphuric acid. Higher temperatures and larger amounts of sulphuric acid cause such differences to become smaller and eventually to disappear. Based on these observations, a simple method has been devised for determination of cholesterol esters and total cholesterol in serum or plasma. The Liebermann-Burchard reaction, carried out at 0° C.

in the presence of 0.025 cc. sulphuric acid, is utilized for cholesterol ester determinations. These substances develop appreciable color intensities under such conditions, while free cholesterol produces very little color. Cholesterol oleate or palmitate solutions serve as standards for colorimetry. A correction is applied for color formed by free cholesterol.

Total cholesterol is found by warming the solutions to 38° C. for 30 to 40 minutes. Free and esterified cholesterol now yield equivalent concentrations of color, proportional to the total cholesterol contained in each solution.

Known mixtures of cholesteryl oleate and cholesterol have been analyzed correctly by this procedure. Cholesteryl oleate added to alcohol-ether extracts of serum can be recovered with fair success. Cholesterol ester determinations by the new method agree with results of gravimetric digitonin estimations. Total cholesterol figures are slightly high, particularly in jaundice.

Coprostenol (allocholesterol) if present, would be determined as cholesterol ester. The close agreement between colorimetric ester analysis and gravimetric determinations indicate that this substance does not exist in plasma. However, loss of coprostenol has not been entirely excluded.

The Secretion of Dyestuffs by the Kidney.—R. Höber (Marine Biological Laboratory, Wood's Hole and Laboratory of Physiology, University of Pennsylvania). The tubules of the aglomerular kidney of the toadfish are permeable to a number of diffusible acid dyestuffs. After intramuscular injection some of them (Orange R, Azofuchsin S, Brillantorange R, Tropaeolin 0002, Echtrot A, Ponceaurot and Indigocarmin) are concentrated in the lumina to such a degree that they appear as deeply colored threads in strong contrast to the colorless or faintly colored epithelial walls. The normal appearance of functional dyestuff concentration in the frog's kidney does not differ from that in the kidney of the toadfish. The usually observed picture after the injection of a dyestuff into the frog, significant by the accumulation of a great number of brightly colored granules in the epithelium of the proximal convoluted tubules, is the result of abnormal conditions, the granules representing dead spaces in the epithelial body. As in the toadfish, the acid dyestuffs enter the cells of the proximal tubules in the frog from the side of the venous capillaries and not from the side of the lumina; this can be demonstrated by injection of Diaminreinblau or Benzoblau 3B, two dyestuffs which cannot pass through the glomeruli, but are found to be stored in the cells of the proximal tubules.

Note on Reflex Thresholds in the Cat During Spinal Shock.—G. P. McCouch, W. J. Snape, and W. B. Stewart (Laboratory of Physiology, University of Pennsylvania). Divinyl ether, due to its rapid elimination, is a suitable anesthetic for transection designed for the study of the initial phase of spinal shock.

The transient depression following spinal transection under divinyl ether in the full grown cat involves the reflex thresholds studied in the following order of severity: ipsilateral extension elicited from the exter-

nal aspect of the thigh, little or not at all; ipsilateral flexion, relatively little; crossed flexion, moderately; crossed extension, severely.

Of these reflexes, the first three are present immediately after transection. Crossed extension may appear at any interval from 20 minutes to more than 24 hours. The lateness of its appearance is probably due partly to spinal shock, partly to inhibition from the crossed flexion reflex. Similarly, the ipsilateral flexion reflex, though relatively little affected by shock, does not extend its receptive field effectively over that of the still less involved antagonistic reflex from the external aspect of the thigh for several days after transection.

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